Preface

This first of two special issues of *Translational Lung Cancer Research* (*TLCR*) includes some of the key presentations at the 10th bi-annual congress of the Spanish Lung Cancer Group (SLCG) in Barcelona in November 2013.

Ten years after the discovery of *EGFR* mutations treatment of non-small-cell lung cancer (NSCLC) with *EGFR* mutations is still single EGFR TKI monotherapy (1,2). The SLCG performed the first large-scale screening of *EGFR* mutations in NSCLC for erlotinib therapy (3). We also observed that BRCA1 was an independent prognostic marker of progression-free survival (PFS) in a subgroup of patients in whom mRNA expression was examined in paraffin-embedded tumor tissue. Patients with low BRCA1 mRNA expression had significantly longer PFS (4). This observation raises the hypothesis that combination with a PARP inhibitor could cause a significant therapeutic benefit based on the concept of synthetic lethal combinations (5). The contribution from Garcia Campelo *et al*. describes the phase I SLCG trial combining gefitinib plus olaparib (PARP inhibitor) in *EGFR* mutant NSCLC patients. This trial is one of the first examples of combining targeted therapy for treatment of *EGFR* mutant patients and the information reported could contribute to highlighting the relevance of combinatorial therapies in the setting of lung cancer with *EGFR* mutations.

EML4-ALK rearrangement is one of the novel subclasses of adenocarcinomas which constitutes and effective therapeutic target. A number of small molecular inhibitors of ALK kinase have been developed and crizotinib is currently used in clinical practice. Intriguingly, one observation indicates a high frequency of EML4-ALK rearrangements in thyroid cancer from atomic bomb survivors in Japan detected by a highly sensitive RT-PCR assay from archival paraffin blocks and not confirmed by FISH or other methods (6). Teixido *et al*. deal with the diagnostic techniques for EML4-ALK fusions since the current method by FISH does not detect some cases with low expression of the EML4-ALK fusion. They establish the basis for comparing FISH with immunostaining and RT-PCR. Also, RT-PCR could have additional advantages for monitoring ALK positive cases in blood.

One of the most intriguing signaling pathways is the HIPPO-YAP; since the discovery of this pathway, increasing information on the relevance of multiple components has come to light, including on the oncogenic role of YAP and activation of several important receptors such as AXL which could be very important for targeted therapies. Felley-Bosco and Stahel have performed a very comprehensive review of this signaling pathway. Drive alterations of this pathway have been well documented in mesotheliomas and primary liver cancers. However, the relevance of the pathway is central to lung cancer and this review can pave the way for further research in this field.

Provencio and Sanchez cover the new field of treatment in the radiotherapy setting, describing several signaling pathways activated in lung cancer which can cause radioresistance. They review the most relevant components of the frequently deregulated pathways including EGFR and other important oncogenic hubs such as mTOR, HSP90 and others and the potential targeted therapies that can be combined with chest irradiation.

Needless to say that surgery is still central to curability of early stage lung cancer and Romero *et al*. therefore review here the importance of number of lymph nodes that can be removed during surgery. This is a unique opportunity to understand how important the number of resected lymph nodes is for potential curability, as well as to evaluate the prognostic value.

Circulating lung cancer cells are being investigated in many classes of tumors and gene expression analysis in circulating tumor cells (CTCs) could be very relevant for genotyping and gene expression analysis. Also, gene expression analysis can provide a unique opportunity to assess the dormant state of viable CTCs. Nel *et al*. under the guidance of Hoffman provide their experience in individual profiling of CTCs in advanced NSCLC patients receiving platinum-based chemotherapy. Their unique experience can further encourage research in this field to overcome the hurdles for routine clinical implementation. This is still a tantalizing area of research in which the Nel review is of great relevance for further understanding the possible mutational heterogeneity between tumor tissue and CTCs which should be considered for future trials of targeted therapy and for monitoring response.

Karachaliou *et al*. review their experience in the field of developing companion diagnostics for treatment selection and the mechanisms of resistance related to *EGFR* mutations along the lines that have previously been reported (5). This review is highly comprehensive and can facilitate understanding of the biology of cancer.

For decades age has been one of the exclusion criteria in clinical trials. Patients older than 65 years old have long been

ruled out from receiving chemotherapy. There are many issues surrounding age and the number of patients over 75 or 80 years old is growing. Co-morbidities are quite frequent among such patients and the role of chemotherapy could be of great benefit for elderly lung cancer patients. Also, some genetic alterations are related to age and Vergenegre *et al*. illustrate their considerable experience in this field, based mainly on the persistent work performed by the French Lung Cancer Group (GFPC). Their review is highly recommended for an understanding of these issues.

We are convinced the reader will find all the topics included in this first special issue and will find this engaging and informative reading.

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doi: 10.3978/j.issn.2218-6751.2014.03.04
Disclosure: The authors declare no conflict of interest.
View this article at: http://www.tlcr.org/article/view/2248/2882

Cite this article as: Rosell R, Massuti B, Karachaliou N. Preface. Transl Lung Cancer Res 2014;3(2):64-65. doi: 10.3978/j.issn.2218-6751.2014.03.04

