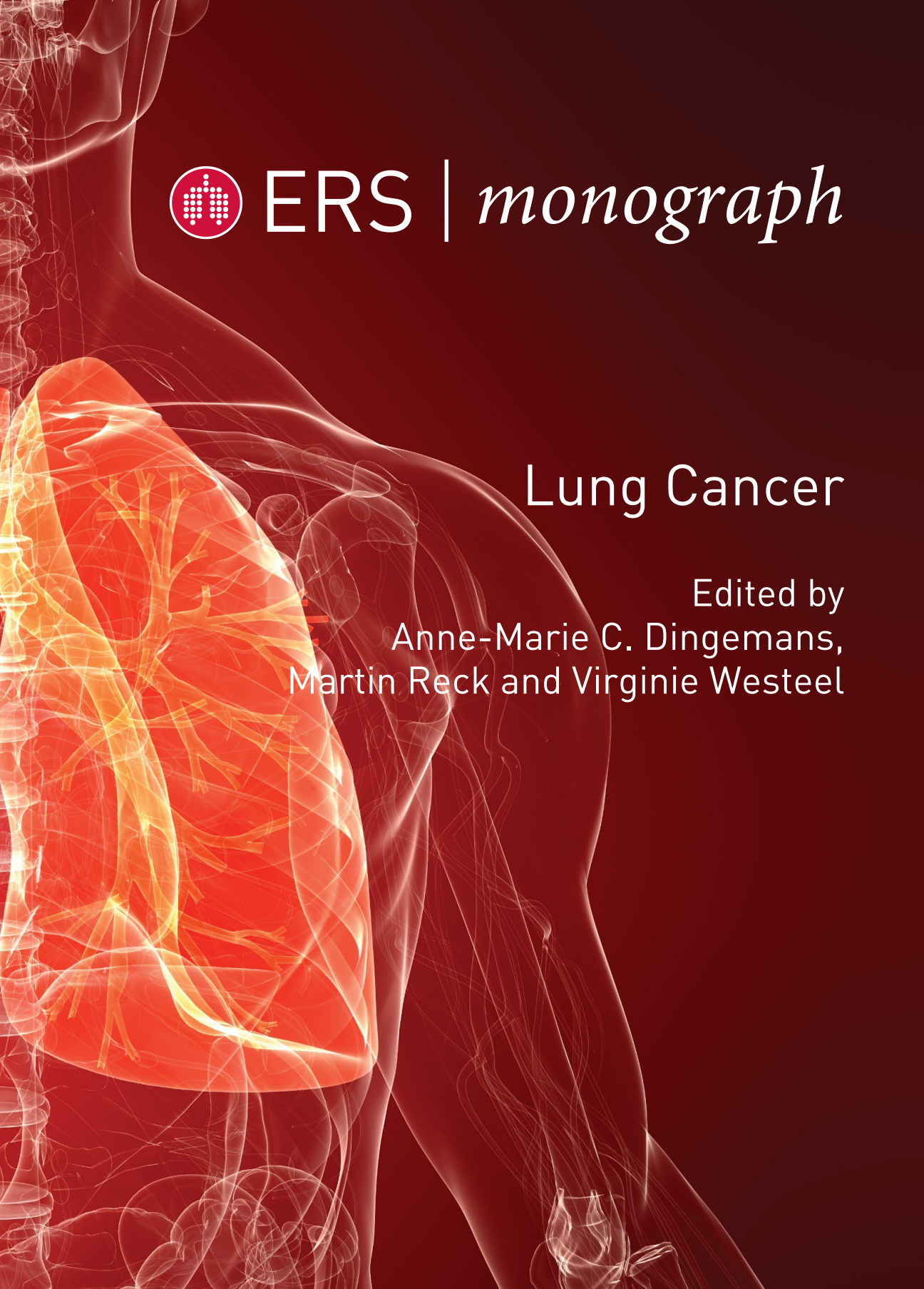

ERS | *monograph*

Lung Cancer

Edited by
Anne-Marie C. Dingemans,
Martin Reck and Virginie Westeel

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Editor in Chief
Tobias Welte

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Contents

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Preface

Tobias Welte, Editor in Chief

The GLOBOCAN project (http://www.globocan.iarc.fr) is a comprehensive cancer surveillance database managed by the International Association of Cancer Registries (IACR) and supported by the World Health Organization (WHO). The project aims to provide up-to-date estimates of the incidence, mortality and prevalence of major cancer types, at a national level, for 184 countries. GLOBOCAN estimate that ~14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide [1]. There were estimated to be 1.8 million new lung cancer cases in 2012 (12.9% of the total), 57% (65% of cancer deaths worldwide) of which occurred in the less developed regions, making lung cancer the most common cancer in the world. In both more and less developed countries, lung cancer is the leading cause of cancer death among males, with the highest estimated age-standardised incidence rates occurring in Central and Eastern Europe (53.5 per 100 000) and Eastern Asia (50.4 per 100 000). In more developed countries, lung cancer has surpassed breast cancer as the leading cause of cancer death among females. The highest estimated rates in females are in northern America (33.8) and northern Europe (23.7), with a relatively high rate in Eastern Asia (19.2) and the lowest rates in Western and Middle Africa (1.1 and 0.8 per 100 000, respectively) [1].

Lung cancer is the most common cause of death from cancer worldwide; it is estimated that it causes nearly one in five deaths (1.59 million deaths, 19.4% of the total). Its high fatality (it has an overall the overall mortality to incidence ratio of 0.87) and the relative lack of variability in survival in different regions of the world, mean that the geographical patterns of mortality closely follow those of incidence. Even so, most lung cancer patients are diagnosed late, with the majority of them at an advanced disease stage. There are currently no curative therapy options available and long-term survival amongst lung cancer patients is still low.

Nevertheless, enormous progress has been made during the last decade. Multimodal therapies have improved the prognosis as has the development of new surgical techniques, the optimisation of

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radiation therapy and the introduction of new chemotherapeutic agents. However, the decisive breakthrough has been the development of new immunopathological techniques, which allow for the detection of special genetic mutations and initiate individualised therapy according to this finding. The number of patients who benefit is still small; however, the quality of life and survival rates of those who respond to this treatment are impressive. The pharmaceutical industry invests heavily in the development of new diagnostic tools and effective treatment modalities, so expectations for the future are great.

Smoking is still the most important risk factor worldwide. The set-up of preventive measures to reduce the smoking rate is therefore of paramount importance. However, some measures must be viewed with a critical distance. The dissemination of electronic cigarettes all over the world is viewed critically by experts and most of the lung societies [2]. The long-term consequences of these devices must be carefully examined before a final assessment is possible.

Thoracic oncology plays an increasingly important role in respiratory medicine, as well as in the European Respiratory Society (ERS). Knowledge about oncology must make up a substantial part of a respiratory physician's training, not only for those working in a hospital, but also for those in an outpatient setting.

This issue of the *ERS Monograph* provides a comprehensive overview of the current knowledge of lung cancer in clinical practice and research. The Guest Editors have done great job of ensuring that all aspects of this complex disease are represented, meaning this book will be of interest to a very broad readership.

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Guest Editors

Anne-Marie C. Dingemans

Anne-Marie C. Dingemans has been associate professor of pulmonology at the Maastricht University Medical Center (Maastricht, the Netherlands) since 2004, where she currently she coordinates clinical lung cancer trials and is involved in translational research on lung cancer.

Anne-Marie Dingemans received her medical degree at Maastricht University (Maastricht) in 1994 and subsequently her PhD at VU Medical Center (Amsterdam, the Netherlands) in 2000 for laboratory research on resistance to chemotherapy in lung cancer. She performed her training as a pulmonologist at VU Medical Center and at Leiden University Medical Center (Leiden, the Netherlands).

Anne-Marie is a board member of the Netherlands Respiratory Society (NRS) and the secretary of the NVALT studies foundation. She is also a member of the Lung and Other Thoracic Tumours faculty of the European Society for Medical Oncology (ESMO), and of the Harmonised Education in Respiratory Medicine for European Specialists (HERMES) Thoracic Oncology task force. Anne-Marie is a member of the American Association of Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), the International Association for the Study of Lung Cancer (IASLC) and the European Thoracic Oncology Platform (ETOP). She has (co)-authored more than 80 publications and book chapters.

Martin Reck

Martin Reck is head of the Department of Thoracic Oncology and head of the Clinical Trial Department in the Department of Thoracic Oncology at the Lung Clinic Grosshansdorf (Grosshansdorf, Germany). He is also Principal Investigator at the Airway Research Center North (ARCN) (Lung Clinic Grosshansdorf), which is a member of the German Centre for Lung Research (DZL).

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

Martin Reck has acted as a Principal Investigator or Co-Principal Investigator in various clinical trials since 1993. His main interests are new medical treatments for thoracic malignancies and translational research related to predictive markers. A particular focus of his work is the clinical development of antiangiogenic compounds, such as bevacizumab, nintedanib and other compounds. Recently, he also has been deeply involved in several key trials with immunotherapies, including ipilimumab, programmed cell death protein-1 and programmed cell death ligand-1 antibodies and other agents.

In addition to the International Association for the Study of Lung Cancer (IASLC), Martin Reck is also a member of the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), the German Working Group for Lung Cancer, the German Cancer Society (DKG) and the German Respiratory Society (DGP). He has published papers in numerous peer-reviewed journals and is member of the Editorial Boards of the *Journal of Thoracic Oncology*, *Annals of Oncology* and *Lung Cancer*.

Virginie Westeel

Virginie Westeel is professor of pulmonology at the University of Franche-Comté (Besançon, France) and head of the Thoracic Oncology unit at the University Hospital of Besançon (Besançon).

She is a graduate of the University of Franche-Comté. Her clinical and research activities are exclusively dedicated to lung cancer and her research interests include lung cancer therapeutics, follow-up and evidence-based medicine.

Virginie Westeel is currently the Principal Investigator of the only large multicentre randomised trial that has been conducted to date on follow-up after lung cancer surgery. Her 93 publications mostly include the results of clinical trials in both early stage and advanced lung cancer.

Virginie Westeel took on the role of Joint Coordinating Editor of the Cochrane Lung Cancer Review Group in 2013. She led the

development of the French guidelines for lung cancer staging. She has been a member of the scientific committee of the French research group, the Intergroupe Francophone de Cancérologie Thoracique (IFCT), from 2009 to 2013, and she is currently a member of the executive committee of IFCT. Virginie was also a member of the scientific committee of IASLC between 2005 and 2009, and of the scientific committee of several World Conference on Lung Cancer (WCLC). She is a member of the American Society of Clinical Oncology (ASCO) and the International Association for the Study of Lung Cancer (IASLC).

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Introduction

Martin Reck[1], Anne-Marie C. Dingemans[2] and Virginie Westeel[3]

Lung cancer still represents one of the most frequent solid tumours with the highest tumour-associated mortality and increasing global incidence rates.

Relevant changes have been seen in epidemiology and there have been substantial improvements in all disciplines of lung cancer treatment. However, the picture of lung cancer treatment has become quite complex, and treatment strategies are moving more and more from global treatment algorithms to individualised treatment.

Standardised and adequate histological, as well as molecular classification (as it is reflected in the recommendations for ADC classification), have become crucial in order to give the individual patient the chance of optimal treatment.

As well as relevant steps in surgery and radiotherapy, new impressive opportunities in systemic treatment have opened up through the identification of treatable oncogenic driver alterations and the appropriate targeted therapies. Furthermore, in 2015, after decades of negative trials, we are experiencing a fascinating phase of immunotherapy with a completely new class of agents.

Of all the solid tumours, lung cancer has really demonstrated rapid and substantial progress in treatment efficacy based on major progress in diagnostics. Therefore, it is of paramount importance that the pulmonologist as key member of the interdisciplinary team is familiar with the current state of the art in lung cancer care.

We hope that this issue will be of interest to all researchers, clinicians and surgeons in the respiratory field and that it will help to improve understanding about lung cancer, answering all the questions encountered in everyday practice.

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List of abbreviations

ADC	Adenocarcinoma
ALK	Anaplastic lymphoma kinase
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CTLA4	Cytotoxic T-lymphocyte antigen 4
D_{LCO}	Diffusing capacity of the lung for carbon monoxide
EBUS	Endobronchial ultrasound
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EGFR-TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
EUS	Endoscopic ultrasound
FEV1	Forced expiratory volume in 1 s
FGFR	Fibroblast growth factor receptor
FISH	Fluorescence *in situ* hybridisation
FVC	Forced vital capacity
HER2	Human epidermal growth factor receptor 2
HGF	Hepatocyte growth factor
IHC	Immunohistochemistry
LCNEC	Large cell neuroendocrine carcinoma
NGS	Next-generation sequencing
NSCLC	Nonsmall cell lung cancer
PET	Positron emission tomography
PFS	Progression-free survival
SCC	Squamous cell carcinoma
SCLC	Small cell lung cancer
TGF	Transforming growth factor
TKI	Tyrosine kinase inhibitor
VATS	Video-assisted thoracoscopic surgery
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor