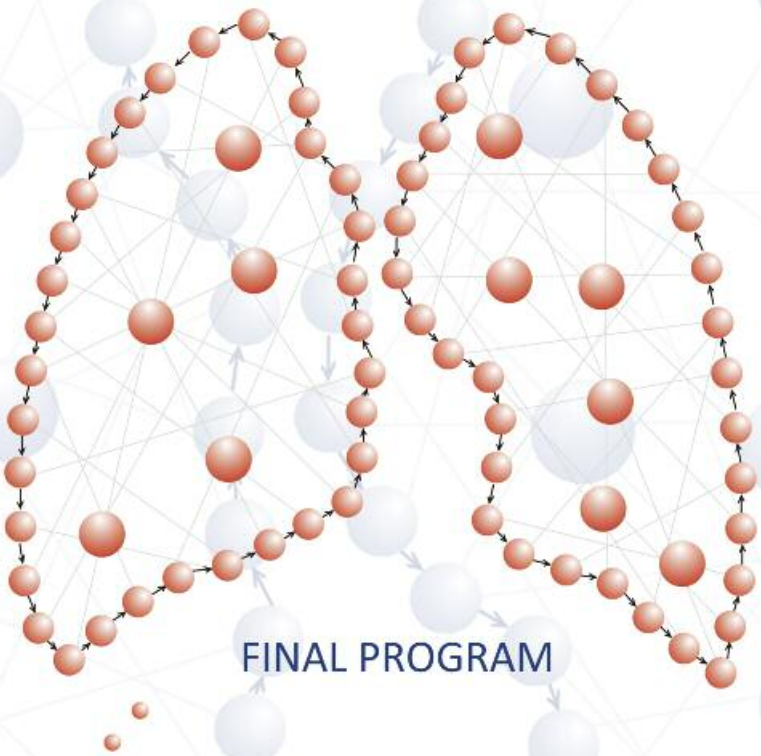
Organized by: Oncology Center of Biomedical Education and Research
Oncology Unit GPP, Athens School of Medicine

3rd LUNG CANCER Network

«From the Bench to the Bedside»



FINAL PROGRAM

31st JANUARY - 1st FEBRUARY 2014

Hilton Athens Hotel, Athens, Greece

Accreditation from:
European Society for Medical Oncology (ESMO)
Panhellenic Medical Association

Under the auspice of:

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

IASLC
International Association for the Study of Lung Cancer

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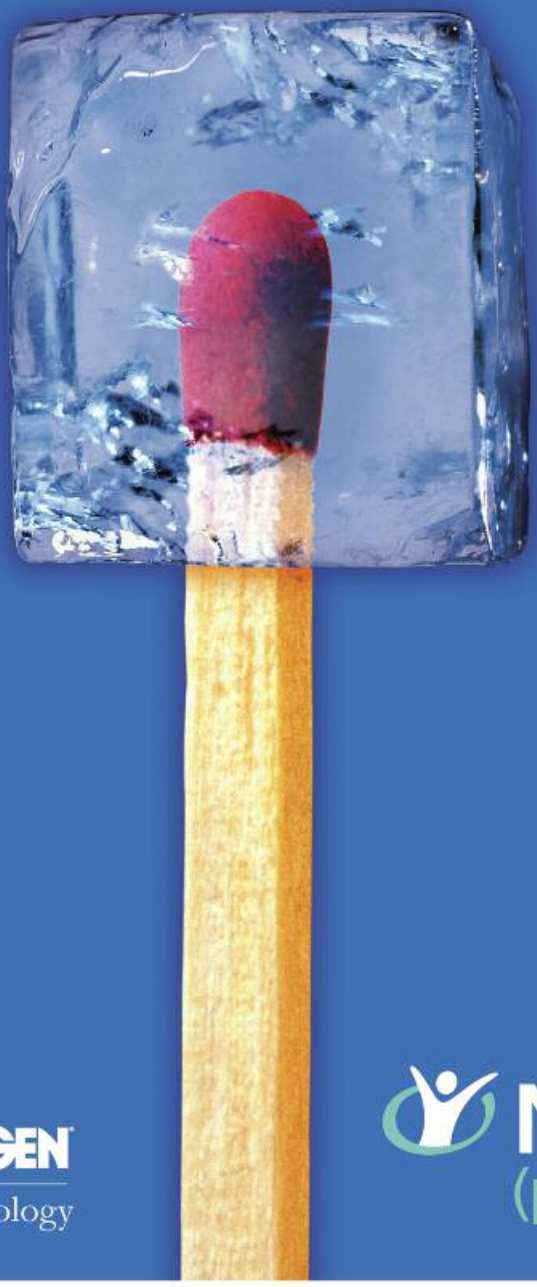
Information | Research



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Βοηθήστε να γίνουν τα φάρμακα πιο ασφαλή:
Συμπληρώστε την **"ΚΙΤΡΙΝΗ ΚΑΡΤΑ"**

Αναφέρατε:
Κάθε ύποπτη ανεπιθύμητη ενέργεια σύμφωνα με το εθνικό σύστημα αναφοράς στο Τμήμα Ανεπιθύμητων Ενεργειών του Εθνικού Οργανισμού Φαρμάκων (ΕΟΦ) Τηλ. 2132040380, Fax 2105549585, με τη χρήση της Κίτρινης Κάρτας διαθέσιμη και στην ιστοσελίδα του ΕΟΦ, www.eof.gr για έντυπη ή ηλεκτρονική υποβολή ή εναλλακτικά στην AMGEN Ελλάς Φαρμακευτικά Ε.Π.Ε. Τηλ.: +30 210 3447000.

NO-GRC-AMG-089-2013- March-P

Content

Invitation Letter

The recent, increasing amount of knowledge regarding lung cancer, especially in the field of basic science, holds promise for personalized treatment of these patients that would provide more effective and less toxic therapeutic approaches, improving the prognosis of the patients with thoracic malignancies. On the other hand, the immense bulk and the rapid recycling of the new information makes difficult its understanding, evaluation and interpretation by the clinicians. Therefore, the "translation" of our recently acquired knowledge from the lab bench to the bedside is neither smooth nor is it without obstructions, due to the existing "gaps" in our understanding and the often contradictory "signals" from clinical trials.

The success of our two previous meetings has prompted us to organize the **3rd Lung Cancer Network: "From the Bench to the Bedside"**. Our aim is to narrow the distance between the bench lab and the patient's bed, between the clinical trials outcome and the routine practice, by bringing together basic scientists, clinical researchers and lung cancer specialists. Our multidisciplinary, international faculty will present the latest clinical data and provide treating physicians with practical information regarding the clinical significance of the histological, molecular and genetic profile of the tumor and how the implementation of targeted agents in the therapeutic algorithm changes the clinical practice of lung cancer patients.

Finally, we anticipate that our meeting, with the presence of our distinguished faculty, would provide the opportunity and motivation for discussions regarding the emerging therapies and set the pavement for the future research and strategies towards the personalized treatment of lung cancer patients.

We cordially welcome you all in Athens in January 31st & February 1st 2014 for a stimulating, innovative and educational meeting.

Learning Objectives

At the conclusion of our educational meeting, the participant will be able to:

- Recognize the clinical significance of molecular genotyping of lung cancer patients
- Understand the molecular pathways that hold promise for therapeutic intervention in lung cancer patients
- Discuss the optimal methodology of clinical trials in the era of translational research
- Recognize the importance of a multidisciplinary approach to the care lung cancer patients

Topics

- End points of translational research clinical trials
- Prognostic and predictive tumor markers
- The molecular pathology of non-smoker lung cancer patients
- Gender discrepancies in lung cancer
- NSCLC driver oncogenes
- EGFR mutation heterogeneity
- Newer generation TKIs inhibitors
- The Met, K-ras and mTOR/PI3K pathways

Target Audience

The meeting is designed for medical, radiation and surgical oncologists, pathologists, chest physicians, scientists, residents-in-training, fellows and other health care professionals interested in the basic and clinical research as well as in the management of thoracic cancers.

CME Accreditation - Auspice

The content of the meeting will be submitted for CME accreditation and we will request the auspice of ESMO, IASLC and ETOP.

The Chairs of the Meeting

Professor Kostas Syrigos

Professor Alex Adjei

Professor Rolf Stahel

Scientific Program

FRIDAY, January 31st 2014

15:30-16:00 Registrations

16:00-17:30 **Challenges for the pathologist and molecular biologist in the era of personalized medicine**
Chair: ***Alex Adjei, Jean-Yves Douillard***
16:00-16:20 Optimal tissue acquisition and minimal requirements. ***Keith Kerr***
16:20-16:40 The WHO classification on adenocarcinoma. ***Elisabeth Brambilla***
16:40-17:00 The RAS challenge in lung cancer. ***Amir Onn***
17:00-17:30 Discussion

17:30-18:00 ***Coffee Break***

18:00-20:00 **Lung cancer clinical trials in the era of translational research**
Chair: ***Rolf Stahel, Kostas Syrigos***
18:00-18:20 Coordinating the pathology lab with the clinical practice. ***Niki Karachaliou***
18:20-18:40 Clinical trials endpoint: OS vs PFS. ***Jean-Yves Douillard***
18:40-19:00 NSCLC prognostic and predictive markers. ***David Rimm***
19:00-19:20 The evolving treatment landscape of NSCLC. ***Alex Adjei***
19:20-19:40 Translating lung cancer biology to the clinic. ***Adi Gazdar***
19:40-20:00 Discussion

20:00-20:15 **Opening Ceremony**
Chair: ***Kostas Syrigos, Rolf Stahel***
Welcome addresses
Honorary award for their contribution to cancer patients.
Jean-Pierre Armand, Adi Gazdar

20:15-20:45 **Opening Lecture**
Early clinical development, a critical moment for drug success.
Jean-Pierre Armand

21:00 Welcome Reception

SATURDAY, February 1st 2014

09:00-10:00 **Immunotherapy of lung cancer**
Chair: ***Solange Peters, Martin Reck***
09:00-09:20 Advances in vaccines immunotherapy. ***Johan Vansteenkiste***
09:20-09:40 Anti-PD-1/Anti-PDL-1 antibodies in NSCLC. ***Luis Paz-Ares***
09:40-10:00 Discussion

Sponsored by Bristol-Myers Squibb

10:00-11:00 **Targeting the neovasculature in adenocarcinomas**
Chair: ***Giorgio Scagliotti, Johan Vansteenkiste***
10:00-10:20 The expanding role of bevacizumab. ***David Planchard***
10:20-10:40 Angiogenesis inhibition beyond bevasizumab. ***Martin Reck***
10:40-11:00 Discussion

SATURDAY, February 1st 2014

11:00-11:30	*Coffee Break*
11:30-13:00	**The EGFR pathway in lung cancer**
	Chair: ***Luis Paz-Ares, Fred Hirsch***
11:30-11:50	Cetuximab in NSCLC: lessons for all. ***Robert Pirker***
11:50-12:10	Current status of EGFR TKIs. ***Filippo de Marinis***
12:10-12:20	Mechanisms of resistance to EGFR TKI and treatment strategies. ***Rolf Stahel***
12:20-12:40	Targeting HER2 and BRAF. ***Solange Peters***
12:40-13:00	Discussion
13:00-14:00	**The EML4/ALK fusion protein**
	Chair: ***Adi Gazdar, Enriqueta Felip***
13:00-13:15	EML4/ALK pathway. ***Ruth Palmer***
13:15-13:30	Detection and monitoring of ALK- rearranged CTCs in ALK positive patients under treatment. ***David Planchard***
13:30-13:45	Optimal therapeutic algorithm for patients with EML4-ALK-positive disease. ***Giorgio Scagliotti***
13:45-14:00	Strategies to overcome crizotinib resistance. ***Anne Chiang***
14:00-15:30	**Symposium**
14:00-14:05	Welcome. ***Kostas Syrigos***
14:05-14:15	Expanding the use of bevacizumab in patients with comorbidities: a case report. ***Kostas Syrigos***
14:15-14:35	Prolonging life expectancy: setting new hallmarks in the first-line adenocarcinoma. ***David Planchard***
14:35-14:45	Optimal use of targeted therapies in NSCLC: a case report. ***Kostas Syrigos***
14:45-15:05	The role of EGFR-TKIs in patients with EGFR wild-type NSCLC. ***Martin Reck***
15:05-15:25	The clinical relevance of MET pathway in NSCLC. ***Hartmut Koeppen***
15:25	Close. ***Kostas Syrigos***

Sponsored by Roche

15:30-16:30	*Break*
16:30-18:00	**Molecular biology of lung cancer**
	Chair: ***Rolf Stahel, Silvia Novello***
16:30-16:50	The clinical significance of circulating tumor cells. ***Wilfried Eberhardt***
16:50-17:10	The clinical significance of the MET pathway. ***Enriqueta Felip***
17:10-17:30	The clinical significance of the K-ras pathway in NSCLC. ***Anne Chiang***
17:30-17:50	The clinical significance of the PI3K pathway in NSCLC. ***Alex Adjei***
17:50-18:00	Discussion
18:00-18:30	*Break*
18:30-20:00	**Personalized treatment on lung cancer patients**
	Chair: ***Alex Adjei, Kostas Syrigos***
18:30-18:50	Squamous cell carcinomas. ***Rafal Dziadziuszko***
18:50-19:10	Small cell lung cancer. ***Andrea Ardizzoni***
19:10-19:20	Neuroendocrine tumors of the lung. ***Dan Granberg***
19:20-19:40	Gender discrepancies of lung cancer. ***Silvia Novello***
19:40-20:00	Discussion
20:00	**Closing Ceremony**

Faculty

Alex A. Adjei
MD, PhD, Professor and Chair, Department of Medicine Katherine Anne Gioia, Chair in Cancer Medicine Senior, Vice-President for Clinical Research Roswell Park Cancer Institute, USA

Andrea Ardizzoni
Dr, Head of Medical Oncology, University Hospital of Parma, Italy

Jean-Pierre Armand
Dr, MD, MSc, Medical Oncologist, Senior Consultant Oncology at Institute Curie and Institute Gustave Roussy, France

Elisabeth Brambilla
Professor of Pathology, Grenoble University Hospital, University Joseph Fourrier Grenoble, France

Anne Chiang
MD, PhD, Assistant Professor, Department of Medicine, Yale University, School of Medicine, Chief Medical Officer, Smilow Cancer Hospital Network, USA

Filippo de Marinis
MD, Director, Thoracic Oncology Division, European Institute of Oncology (IEO), Milan, Italy

Jean-Yves Douillard
MD, PhD, Professor of Medical Oncology, Senior Staff Physician, Integrated Centers of Oncology René Gauducheau, France, Chair of Educational Committee ESMO

Rafal Dziadziuszko
Professor of Medicine, Deputy Chair, Department of Oncology and Radiotherapy, Medical University of Gdansk, Poland

Wilfried Eberhardt
Dr, Department of Medical Oncology, West German Cancer Centre, University Hospital Essen, University Duisburg-Essen, Germany

Enriqueta Felip
MD, PhD, Head, Thoracic Oncology Unit, Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Adi Gazdar
Professor of Pathology and Deputy Director, Hamon Center for Therapeutic Oncology Research, The W. Ray Wallace Distinguished Chair in Molecular Oncology Research, University of Texas Southwestern Medical Center, USA

Dan Granberg
Dr, MD, PhD, Associate Professor, Senior Consultant, Department of Endocrine Oncology University Hospital, Uppsala, Sweden

Fred R. Hirsch
MD, PhD, Professor of Medicine and Pathology, Associate Director for International Programs, University of Colorado Cancer Center, USA

Niki Karachaliou
Dr, Instituto Oncológico Dr. Rosell (IOR), Dexeus-Quiron University Hospital, Barcelona, Spain

Keith Kerr
Professor, Consultant Pathologist, Department of Pathology, Aberdeen Royal Infirmary, Professor of Pulmonary Pathology, Aberdeen University Medical School, Foresterhill, Aberdeen, UK

Koeppen Hartmut
MD, PhD, Staff Pathologist, Genentech

Silvia Novello
MD, PhD, Assistant Professor, Thoracic Oncology Unit, University of Turin, AUO San Luigi, Italy

Amir Onn
MD, Head, Department of Pulmonary Medicine and Pulmonary Oncology, Sheba Medical Center, Israel

Ruth Palmer
PhD, Professor in Molecular Genetics, Department of Molecular Biology, Umeå University, Sweden

Luis Paz-Ares
Dr, Chair of Oncology Department, Hospital Universitario Virgen del Rocío/Instituto de Biomedicina de Sevilla, Spain

Solange Peters
MD, PhD, PD-MER, Department of Oncology, University of Lausanne, Switzerland

Robert Pirker
Dr, Professor of Medicine, Program Director for Lung Cancer, Department of Medicine I, Medical University of Vienna, Austria

David Planchard
MD, PhD, Associate Professor, Pulmonary-Oncologist, Department of Medical Oncology, Thoracic Group, Gustave-Roussy, France

Martin Reck
Dr, MD, PhD, Head of Department of Thoracic Oncology and Department of Clinical Trials, LungClinic Grosshansdorf, Member of the German Research Institute for Lung Research (DZL), Germany

David Rimm
MD, PhD, Professor, Director of Translational Pathology, Yale University School of Medicine, USA

Giorgio Scagliotti
Dr, Professor of Oncology, Head Department of Oncology, University of Torino, Italy

Rolf Stahel
MD, Head of the Center for Lung and Thoracic Oncology, Senior Staff Physician, Clinic of Oncology, University Hospital of Zürich, Titular Professor of Medicine, University of Zürich, Switzerland

Kostas Syrigos
MD, PhD, Professor and Head, Oncology Unit GPP, Athens School of Medicine, Visiting Professor of Thoracic Oncology, Yale School of Medicine, CT, USA

Johan Vansteenkiste
Dr, MD, PhD, Head of Clinic, Respiratory Oncology Unit, University Hospital KU Leuven, Leuven, Full Professor Internal Medicine, Faculty of Medicine, KU Leuven, Belgium

Scientific Information

Audiovisual – Technical Support

The meeting room will be equipped with data video projectors, laser pointers etc, for power point presentations. Technical Support Center will be available outside the "Hesperides" Hall. Technical staff will assist with the presentations. All speakers are kindly requested to submit their presentation at least 1 hour prior to their scheduled presentation.

Language

The official language of the congress is English.

CME Accreditation - Auspice

The content of the meeting will be submitted for CME accreditation. Accreditation will be received from the European Society for Medical Oncology (ESMO) and the Panhellenic Medical Association. The meeting will request the auspice of ESMO, IASLC and ETOP.

Name badges

All registered participants will receive name badges, which they are kindly requested to wear at all times. Each badge will have a barcode for monitoring the hours of attendance.

Certificate of Attendance

All registered participants who have attended at least 60% of the total scientific program will receive a certificate of attendance from the Secretariat Desk after the closing ceremony.

General Information

Organized by the

Oncology Center of Biomedical Education and Research
Oncology Unit GPP, Athens School of Medicine

Meeting website

www.lungcancernetwork.eu

Meeting Dates

31st January – 01st February 2014

Meeting Venue

Hilton Athens Hotel
46 Vassilissis Sofias Avenue
115 28 Athens, Greece
Tel.: 00 30 210 72 81 000

Conveniently situated in the heart of the city's commercial district, and just 25 minutes from the airport using the Athens Metro, the Hilton Athens' prime location and fabulous facilities make it the perfect spot for Athens meetings and exhibitions of all sizes.

The Meeting will take place at the "Hesperides" Hall.
The Meeting Secretariat will operate at the "Hesperides" foyer during the sessions.

Registration Cost

Type of Registration	Cost
Doctors*	400€
Residents	150€
Nurses	100€
Medical students	free

Registration cost includes:

- Admission to all sessions & exhibition area
- Meeting material
- Certificate of attendance
- Opening Ceremony & Welcome Reception
- Coffee breaks

* *ESMO & IASLC Members will receive a 20% discount.*

Please visit the meeting's official site to download the necessary forms.

Meeting's Secretariat

E.T.S. Events & Travel Solutions S.A.
El. Venizelou 154, 171 22 N. Smyrni - Athens, Greece
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Notes

Faculty Biographies

Alex A. Adjei

Alex A. Adjei is Professor of Oncology and Chair of the Department of Medicine at the Roswell Park Cancer Institute (RPCI) in Buffalo, NY, USA as well as Senior Vice-President for Clinical Research. In addition, he holds the Katherine Anne Gioia Chair in Cancer Medicine at RPCI, and is Professor of Medicine and an Academic Scholar in Medicine at the State University of New York in Buffalo. Dr Adjei has served on a number of US National Cancer Institute Lung Cancer Committees. He was Vice-Chair of the North Central Cancer Treatment Group and Lung Cancer Committee Chair. He is currently a member of the Thoracic Malignancies Steering Committee, and vice-chair of the Lung Cancer Translational Science Committee.

Dr Adjei served as Chair of the CTSA Study Section of NIH from 2007-2012, and is a member of the Clinical Oncology Study Section as well as Subcomittee A (reviewing cancer centers) of the National Cancer Institute. He is the Editor-in-Chief of the Journal of Thoracic Oncology and a member of the Board of Directors of the International Association for the Study of Lung Cancer (IASLC).

Dr Adjei's research is focused on pharmacogenetics, experimental therapeutics and clinical drug development. He received the first ASCO Drug Development Research Professorship in 2012 in recognition of his mentorship and his work in cancer drug development. He has authored 210 publications dealing primarily with preclinical pharmacology and phase I trials as well as novel therapeutics/phase II trials of lung cancer.

Andrea Ardizzoni

Dr Ardizzoni has received his medical degree and completed postgraduate course in internal medicine and medical oncology at the University of Genoa, Italy. He has been Deputy Head of Medical Oncology and Chairman of the Lung Cancer Program at National Institute for Cancer Research of Genoa until 2003. Since 2004 he has been appointed as Head of Medical Oncology at the University Hospital in Parma, Italy. Dr Ardizzoni has been Professor of Oncology at the University of Genoa and is currently Contract Professor of Oncology at the University of Parma. He has published over 200 papers in international peer-reviewed journals indexed by PubMed. Dr Ardizzoni has served as Secretary and Quality Assurance Chairman of the EORTC Lung Cancer Group and as Secretary of the Italian Task Force for Lung Cancer (FONICAP). He is also a member of the Italian Association of Medical Oncology (AIOM), ESMO, IASLC and the ESMO and IASLC Educational Committees. Dr Ardizzoni has served as co-ordinator of several clinical and translational studies, mainly in the area of lung cancer and mesothelioma treatment, at national and international level and has received a number of academic research grants from Italian Ministry of Health, Italian Drug Agency, AIRC (Italian Association for Cancer Research). Dr Ardizzoni is also member of Parma University Hospital “Research Board” and of Tuscany Cancer Institute “Advisory Scientific Committee”.

Jean-Pierre Armand

Dr JP Armand ισ s certified in Medical Oncology (University of Toulouse III and Paris XI) that focuses his cancer research in the field of new mechanism of oncogenese and early drug development.

He was recently General Director of the Institut Claudius Regaud in Toulouse (2007 -2012) and is cancer adviser to the Dean of University of Toulouse. Over the last five years he has been in charge of the construction of a new cancer center, in a European research hub created in the Toulouse cancer campus (Institut Universitaire du Cancer).

Although expert in breast, head&neck, and neuro-oncology, the first field of Dr Armand was very early drug development in phase 1 and 2. He has been the founder of the IGR Phase I Unit (Sitep) in the early 80s. He did the first in human phase I in the world at IGR of numerous drugs, including classicals cytotoxics, Irinotecan, Oxaliplatin, Taxotere, Navelbine, Vinflunine, and more recently targeted therapies, Sutent, Sorafenib, Temsirolismus...

He has (co)authored over 300 medical and scientific peer-reviewed articles and he is/was member of the Editorial Boards of Annals of Oncology, the European Journal of Cancer, Journal of Clinical Oncology, Investigational New Drugs, Anticancer Research, Clinical Cancer Research.

- In 2008 (Stockholm) he received the ESMO Award as “the European oncologist of the year”
- In 2013 he received the Targeted Anticancer Therapy (TAT) honorary award in recognition of his contribution to new drug discovery in cancer
- In 2013, he received the nomination of Chevalier of Legion d’Honneur from the French government for life achievement dedicaded to public health in oncology.

After a 5 years as CEO of Institut Claudius Regaud in Toulouse, he is now (2012) back in Paris at the Institut Curie and Institut Gustave Roussy, as senior consultant advisor to the 2 directors, Prof Teillac (Curie) and Prof Eggermont (IGR).

Elisabeth Brambilla

Dr. Elisabeth Brambilla is Professor of Pathology since 1993, expert in lung tumor pathology, nominated as 1st class Professor in 2004 and as exceptional class Professor in 2006. She is currently the Head of the Department of Pathology at the Grenoble University Hospital. She is responsible for pathology teaching at the University Joseph Fourier, Faculty of Medicine since 1999. She is the leader of INSERM research team (Inserm Research Center Institut Albert Bonniot, U823 ; team 2 devoted to Molecular Basis of Lung Cancer Progression) and Head of the Department 2 “Oncogenesis and Biotechnologies” from 2007.

At the frontier between expertise in lung pathology and leadership of INSERM research Unit, her work provided original insight into the functional network of P53 / P14 tumor suppressor gene network in lung cancer with application to the early molecular lesion in bronchial preneoplasia providing tools for early detection. As pathologist she has provided founding descriptions of new pathological entities with clinical significance, has served in the course panel of expert pathologists to provide the revised version of WHO classification of lung tumors in 1999 and was editor and author of the last 2004 Pathology and Genetics of the lung, pleural and thymic tumors. Between 2007-2010, she was co-chair with WD Travis of the Joint Task Force IASLC/ATS/ERS : Multidisciplinary International Classification of Lung Adenocarcinoma She was a recipient of the Mary Matthews Award for lung pathologist in Barcelona 2005 and the Robert Totten Award for Pathologist at Pennsylvania University, Pittsburgh 2010. She was editor of WHO lung tumor classification book in 1999, 2004 an next one 2015.She is author of more than 300 peer-reviewed manuscripts, 18 book chapters and editor of 4 books.

At the interface between pathology and lung biology she is the actual head of assembly of Cell and Molecular Assembly of European Respiratory Society (ERS), member of the Board of ATS Clinical Assembly since 2000, chair of the Pathology Committee of IASLC since 2005, member of the Board of Director of IASLC from 2007 to 2011.

She sustained a track record of public service on several editorial boards (International Journal of Cancer, Respiration, Lung Cancer), is Associate-Editor of Lung Cancer and serve in scientific Advisory Boards of INSERM (clinical research assembly) and several scientific Advisory Boards : ARC, Ligue Contre le Cancer, INCa (Institut National du Cancer). nominated member of the National Commission of University in charge with nomination of Professors in France 2004- 2011 and member of INSERM Commission 6 (2007-2012)

Anne Chiang

Dr. Chiang is an Assistant Professor of Medicine (Medical Oncology) at Yale University. She is a medical oncologist with a background in translational research in metastasis, as well as experience in clinical practice in both academic and community settings. Her specialty is in thoracic oncology and she is involved in clinical research protocols specific to patients with lung cancer, special interest in developing therapeutics for patients with small cell lung cancer. She also serves as the Chief Medical Officer of the Smilow Cancer Hospital network and oversees operations, quality efforts, and clinical research.

She received her BA from Princeton University, PhD in Molecular Genetics from Harvard University, and MD from Weill Cornell Medical School in 1999. She went on to do residency in Internal Medicine at NY Presbyterian Hospital—Columbia University. During her oncology fellowship at Memorial Sloan Kettering Cancer Center, she also did postdoctoral laboratory research in metastasis. She was an attending physician at MSKCC until 2008. She has been at Yale now since 2011. Other interests include quality improvement for cancer services. She has served on the ASCO Quality of Care Committee since 2011 and joined the QOPI Certification Program Oversight Council in 2013.

Filippo De Marinis

Filippo de Marinis is Director of Thoracic Oncology Division in IEO (European Oncology Institute) in Milan.

He has published more than 140 printed scientific works (of which 12 books/monographers, more than 45 on International Indexed Reviews and 100 on Italian reviews). He has presented about 300 scientific works accepted at congresses (about 150 at Italian Congresses and about 150 International Congresses, of which 60 of ASCO). He has participated to more than 250 Italian and International Congresses for oral reports and/or moderations. He has organized more than 60 congresses of scientific updating.

He is active member of 7 Scientific Italian and International Societies in Oncology.
He is University Professor at: School of Specialization in Respiratory Apparatus Diseases at the University "La Sapienza" of Rome;
He is Member of: ILCP (Italian Lung Cancer Project) a Scientific Cooperative Group
He is expert in Good Clinical Practice Trials on "New" Antineoplastic Drugs (Phase I, II and III) and he developped trials on Lung Cancer with Vinorelbine, Paclitaxel, Gemcitabine, Topotecan, Docetaxel,Alimta, Affinitak, MMPI, SR 48692, Gefitinib, Cetuximab, BMS 275183, Bevacizumab etc.

Jean-Yves Douillard

Jean-Yves Douillard is Professor of Medical Oncology at the Integrated Centres of Oncology René Gauducheau and University of Nantes Medical School, both in Nantes, France. He received his medical training at the University of Nantes Medical School before obtaining a fellowship from the French Ministry of Health and the US National Institutes of Health John E. Fogarty International Center for Advanced Study in the Health Sciences in Bethesda, Maryland, USA.

Dr Douillard returned to France in 1981 and became an Assistant Professor in Medical Oncology at the University of Nantes, where he specialised in lung cancer, gastrointestinal oncology and biological therapies, including the use of monoclonal antibodies in human tumours. He spent two additional years at the US Food and Drug Administration's Center for Biologics Evaluation and Research in Bethesda and returned to Nantes where he participated in clinical trials for lung cancer and gastrointestinal tumours, and investigated numerous new drugs and targeted therapies.

Dr Douillard has published numerous articles in various scientific journals, including *The Lancet*, *The New England Journal of Medicine* and *Journal of Clinical Oncology* among others. He has been a member of the editorial boards of the *Journal of Clinical Oncology* and *Bulletin du Cancer*, and currently serves on the editorial board of *Hybridoma*. Dr Douillard is the International Editor of *Clinical Colorectal Cancer*. He is a member of the Association for Cancer Research, Society of Clinical Oncology, European Society for Medical Oncology and is Chairman of the ESMO Educational Committee and member of the International Association for the Study of Lung Cancer and Scientific Board Member of IFCT (Francophone Intergroup of Thoracic Oncology).

Rafal Dziadziuszko

Prof. Rafal Dziadziuszko completed his training in Radiotherapy (2001) and Medical Oncology (2004) at the Department of Oncology and Radiotherapy of Medical University of Gdansk, Poland.

He subsequently completed translational cancer research fellowship at the University of Colorado Cancer Center. Between 2005 and 2007 he worked on predictive assays for EGFR targeted therapies in lung cancer, including immunohistochemistry, gene copy number and activating mutations. He then returned to his home institution to serve as a deputy chair of the department.

Prof. Dziadziuszko's main interests include lung cancer and clinical research methodology, and he is a co-author of several peer-reviewed articles and book chapters on this matter. He is a member of European Organization for Research and Treatment of Cancer – Lung Cancer and Radiotherapy Groups, European Thoracic Oncology Platform, European Society of Medical Oncology, American Society of Clinical Oncology and American Association for Cancer Research. He has also participated in organization of numerous academic clinical research studies in Poland and Central Europe through Polish Lung Cancer Group and serves as the Vice-Chairman of the Central and East European Oncology Group.

His current work includes identification of novel targets for lung cancer trials, novel technologies in radiation therapy of lung cancer and early lung cancer detection.

Wilfried Eberhardt

Dr. med. Wilfried Ernst Erich Eberhardt graduated in Medicine from the University of Duisburg-Essen, Germany, in 1984. He has a clinical training in general internal medicine, medical endoscopy, radiology and medical oncology/hematology from Bethesda Hospital, Essen, as well as University Hospital of Essen, Germany. He has been recipient of a research fellowship grant (short term) of the Japanese Ministry of Health twice in 2000 and 2003 and visited the National Cancer Centre Hospital Tsukiyi, Japan.

Dr. Eberhardt´s research interest has mainly been lung cancer, general thoracic oncology and malignant mesothelioma and his studies have focused on clinical research, new drug development in lung cancer (phase-I, -II, -III, -IV), and multimodality treatment aspects of lung cancer("trimodality"). Recently, his interest has also been translational thoracic oncology and he has been elected deputy speaker of the Clinical Trials Board of the German Consortium for Translational Oncology (DKTK).

He moved to the West German Cancer Centre in 1989 and became Senior Physician of the Department of Medical Oncology in 1997, Consultant for Medical Oncology in 2003, Vice Director for regional affairs of the West German Cancer Centre (WTZ) in 2007, Chief Executive Officer of the Lung Cancer Centre of the WTZ in 2009. At the University of Duisburg-Essen Dr. Eberhardt has focused on multimodality treatment and the clinical drug development program in thoracic oncology. Dr. Eberhardt has been Chair of the International Association for the Study of Lung Cancer (IASLC) Education Committee, member of the Board of Directors of IASLC from 2007 to 2011 and is currently member of the IASLC Staging Committee. He also served on several committees in the American Society of Clinical Oncology (ASCO), twice on the Scientific Programm Committee (Thoracic Tracks) from 2006 to 2008 and from 2011 to 2013.

He is currently member of the Thoracic Oncology Faculty of ESMO. He is currently the Speaker of the Thoracic Oncology Track of the German Working Group for Medical Oncology (AIO). He is member of several Journal Editorial Boards, including Future Oncology, Clinical Lung Cancer, Therapeutic Advances in Oncology, Framingham in Oncology, and Associate Editor for the IASLC journal: Journal of Thoracic Oncology since 2006. Dr. Eberhardt has published more than 115 scientific articles about lung cancer and medical oncology.

Enriqueta Felip

Enriqueta Felip is PI of VHIO's Thoracic Cancer Group, within the Oncology Department, Vall d'Hebron University Hospital, and is also Associate Professor of Medicine at the *Universitat Autònoma de Barcelona*.

She is in charge of management of thoracic cancer patients and responsible for lung cancer trials at the Oncology Department.

Current research lines include the optimization of chemotherapy in early-stage disease, evaluation of new drugs, the investigation into novel pharmacogenomic approaches, and the elucidation of potential mechanisms of resistance to tyrosine-kinase inhibitors.

Enriqueta Felip received her medical degree from the *Universitat Autònoma de Barcelona* (UAB), where she also completed her PhD studies in medical oncology. She is currently a member of the Spanish Lung Cancer Group, the Spanish Society of Medical Oncology, the European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO) and the International Association for the Study of Lung Cancer (IASLC).

She is a member of the Scientific Executive Committee of the National Lung Cancer Partnership and is also the subject editor of Minimum Clinical Recommendations for Diagnosis, Treatment and Follow-up in Lung Cancer for ESMO. She is associate editor of *Annals of Oncology* and *Lung Cancer*. She is author of many peer-review articles and book chapters relating to the field of lung cancer.

Adi Gazdar

Adi Gazdar serves as a professor of pathology and Deputy Director of the Hamon Center for Therapeutic Oncology Research at the University of Texas Southwestern Medical Center. Dr. Gazdar is the holder of the W. Ray Wallace Distinguished Chair in Molecular Pathology Research. He is a pathologist and molecular biologist with a long standing interest in lung cancer with over 400 publications in this field. He is among the most widely quoted scientists in medical literature (current position 231).

He received the Mary Matthews award from the International Association of the Study of Lung Cancer for contributions to pathology excellence. He has extensive experience with tissue procurement and processing and cell culture experience. He has developed a new molecular classification for lung cancers. The cell lines he has initiated are have been widely distributed worldwide and form the basis of much of the in vitro studies on lung cancer. He has closely collaborated with numerous pathologists, investigators and clinicians for many years. He has been a member of the IASLC for over 30 years, and served on the Board of Directors and on the Pathology Panel. He was a member of the IASLC sponsored Committee that reclassified lung adenocarcinomas and serves on WHO committees reclassifying lung cancers.

Dan Granberg

Dr. Dan Granberg is consultant at the Department of Endocrine Oncology, Uppsala University Hospital, which is the only department in the world specializing in taking care of patients with neuroendocrine tumours, and is one of the ENETS Centre of Excellence.

He is specialist in endocrinology and internal medicine and has 22 years' experience in endocrine oncology. He is treating a lot of patients harbouring neuroendocrine tumours – patients referred from all over the world, including European and Asian countries, the United States, Canada and Australia.

During four years, he was responsible for teaching medical students at the Endocrine Oncology Department. In 1995, he was awarded the Regnell prize at the Department of Medicine for his educational work. Over the years, he has given many lectures to medical students, doctors, and patients in Sweden and in other countries.

Dr. Granberg is specially interested in neuroendocrine lung tumours and targeted irradiation therapy. He wrote his doctoral thesis on bronchial carcinoids. He has published more than 40 articles and is the author of a number of book chapters on bronchial carcinoids and neuroendocrine tumours. He is currently involved in several research projects in the field of neuroendocrine tumours.

Fred R. Hirsch

Fred Hirsch is Professor of Medicine and Pathology, University of Colorado, Denver, Colorado, USA and Chief Executive Officer of IASLC.

Professor Hirsch received his MD and PhD from the University of Copenhagen, Denmark. Afetr training in pathology and medical oncology in Copenhagen, he he served from 1996-1999 as chief physician ("overlaege") at the Department of Oncology of the Finsen Center, Rigshospitalet in Copenhagen. from 1999-2002 he was Visiting Professor at the University of Colorado Cancer Center and since 2012 Professor of Medicine and from 2004 also Professor of Pathology at the University of Colorado. Professor Hirsch has extensive teaching experience and has been a supervisor for many European and Asian post-doctoral trainees in his lab at the University of Colorado Cancer Center. .

As an active researcher, he has received numerous grants. His main interest involves research into development and clinical implementation of biomarkers for early detection and therapy in non-small cell lung cancer (NSCLC). Professor Hirsch is a recipient of the Mary J Matthews Distinguished Scientific Award, presented by the International Association for the Study of Lung Cancer (IASLC). He has been in the Board of Directors for IASLC and is now the Chief Executive Director of IASLC. He has been an active member of other scientific and professional bodies, particularly the American Society of Clinical Oncology. He has also been involved in many international symposia and meetings, either as presiding over, or being a member of the organizing committees or as an invited speaker. He has served as member of NCI Steering Committee for Thoracic Malignancies and is currently Chair of NCI/FDA Task Force for developing "Masterprotocols in Lung Cancer".

Professor Hirsch is Associate Editor of Journal of Thoracic Oncology, and section editor of The Oncologist. He is an editorial board member of many oncology journals. He is widely published, having authored 10 books, 30 book chapters and more thant 250 peer-reviewed manuscripts.

Niki Karachaliou

Dr Niki Karachaliou is a Medical Oncologist and she is a member of the Translational Research Unit in the Instituto Oncológico Dr. Rosell (Barcelona).

She was admitted to the University of Athens - Medical School after National Examination in 1994 and she completed her graduate studies (1994-2002) with the score 9/10 (duration of studies: 6 years); afterwards she did her 2-year rural medical practice (2002-2004).

She completed internal medicine residency at the General Hospital of Chalkida in Evoia-Greece (2005-2008), including six months of haematology at the 3rd Dept of University Hematological Department, of Sotiria Hospital in Athens.

Thereafter she completed her fellowship in Medical Oncology at the University Hospital of Heraklion- Crete-Greece (2008 – 2011). In 2010 the elaboration of her PhD Thesis entitled: "Prognostic and/or predictive value of *ERCC1, BRCA1, ATP7B, TOPOI, TOPOIIA, TOPOIIB, PKM2* and *c-MYC* genes in patients with small cell lung cancer (SCLC)" was approved by the council of Medical School, University of Crete (22/03/2010) with Prof. V. Georgoulias being Supervisor. She is the author of 24 papers published in international peer reviewed journals. Specific areas of interest in oncology include translational research in lung cancer and phase I and II clinical trials.

Keith Kerr

Keith Kerr has been a Consultant Pathologist in Aberdeen since 1989, after under and post-graduate training in Edinburgh.

He was awarded an Honorary Chair in Pulmonary Pathology at the University of Aberdeen in 2006.

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 the identification of predictors of therapy response.

He is a member of numerous national and international lung cancer clinical advisory and research groups, including for WHO, IASLC, EORTC and ETOP.

He is a member of the BTOG steering group, the Pulmonary Pathology Society Council, the ETOP Foundation Council and the Board of the IASLC.

He is involved in a number of UK, European and North American initiatives looking at the introduction, operation and quality assurance of guidelines for management of, and molecular pathology testing in, lung cancer.

Silvia Novello

Present position

Since Oct 2010, Assistant Professor, Thoracic Oncology Unit University of Turin, AOU San Luigi-Orbassano

Affiliations to Scientific Societies

Italian Association of Medical Oncology (AIOM), President of WALCE (Women Against Lung Cancer in Europe), International Association for the Study of Lung Cancer (IASLC, since July 2011, Board of Director member), Member of NLCP (National Lung Cancer Partnership) Scientific Committee, American Society of Clinical Oncology (ASCO), member of Innovators in Lung Cancer (limited to 45 young investigators worldwide), Member of the 11th World Conference on Lung Cancer Educational Committee - Barcelona (IASLC), Member of the 12th World Conference on Lung Cancer-South Korea Educational Committee Member of IASLC Young Investigators Award Scientific Committee .

Research Interests

Aspects of basic research and applied clinical research concerning bronchogenic carcinoma (main area of research. Trials in different lung cancer and pleural mesothelioma clinical stages (chemotherapy and therapy options, chemo-surgical and chemo-radiotherapy) subinvestigator or principal investigator in more than 50 phase I/II, II and III clinical trials in the last ten yrs.

Supportive care (antiemetics, hematopoietic growth factors, bisphosphonates). The treatment of lung cancer in elderly patients; Serum and molecular markers dosage and in various biological fluids in lung cancer patients.

Role of cytokines in thoracic malignancies (lung cancer, pleural mesothelioma); determination of proliferative activity of lung cancer, role of oncogenes, antioncogenes, growth factors and their receptors in lung cancer (pathogenesis, prognosis); pharmacogenomics and lung cancer.

Women and lung cancer .

Applied clinical research aspects regarding interstitial lung disease: clinical diagnosis, role of bronchoalveolar lavage, determination of cytokines .

Bibliometric and scientometric data

The research activities have led to the realization of more than 100 scientific papers on international peer reviewed journals and books, some of which as first-, last- or corresponding author; h-index =23; total citation number =3263; average citations per item=27.65.

Amir Onn

Dr. Onn is a graduate of the Hadassah and Hebrew University School of Medicine in Jerusalem, Israel. He completed his residency in internal medicine and fellowship in pulmonary medicine at the Tel-Aviv Sourasky Medical Center. He continued with post-doctoral fellowship and a clinical fellowship in interventional pulmonary oncology at the University of Texas MD Anderson Cancer Center, in Houston, Texas. He then became a member of the faculty of the Department of Pulmonary Medicine at MDACC and as an assistant professor received the prestigious physician scientist grant.

Since his return to Israel in 2006, Dr. Onn has developed the pulmonary oncology service and became the Director of the Department of Pulmonary Medicine and Pulmonary Oncology at Sheba Medical Center, the largest medical center in Israel. Dr. Onn is a co-director of the Sheba Medical Center Institutional Tumor Bank, and the Program Director of the Sheba Medical Center and MDACC Sister Institution Program. In 2010 he initiated the first Israeli multidisciplinary conference on lung cancer, and is the chair of these annual conferences.

Dr. Onn serves as a director of WIN, Worldwide Innovative Networking consortium in personalized cancer medicine, and serves as a global coordinator for tissue procurement and processing for the WINTHER clinical trial. His areas of research interest are lung cancer genomics and the biology of pleural effusion.

Ruth Palmer

Current position
Professor in Molecular Genetics, Umeå University, Umeå, Sweden.

Previous appointments
Human Frontier Science Program (HFSP)
Post-doctoral Research Fellow with Tony Hunter, The Salk Institute, San Diego, USA. Supervisor: Tony Hunter

Doctoral degree (Ph.D.) from the Imperial Cancer Research Fund (now Cancer Research UK), 44 LIF, London. Supervisor: Peter Parker

National and international prizes and awards
Eric K. Fernström prize for young researchers
Svedberg Prize awarded by the SFBM
EMBO Young Investigator

Scientific focus
Dr. Palmers research is predominantly focused on analyzing the functions of the Anaplastic Lymphoma Kinase (ALK) receptor tyrosine kinase. We employ both *Drosophila*, cell culture and mice as models to dissect ALK-activated pathways during developmental processes. Recently we have been employing our accumulated knowledge to investigate their importance in cancer pathogenesis in mammalian cells. We have described the essential role of dALK in the formation of the fly gut muscle during embryogenesis and identified Jellybelly (Jeb) as a bona fide ligand for the dALK receptor. The Jeb-Alk signaling pathway is now known to be important in neuronal development during development, as shown in work from several laboratories. We continue to elucidate the role of signaling pathways downstream ALK, identifying novel molecules which are a target of the ALK signaling network.

Recent focus has turned to ALK in neuroblastoma and in particular the EML4-ALK fusion protein in NSCLC, together with the significance of ALK in these diseases. We are currently studying the function of mammalian ALK in mouse genetic models to study the role of ALK mutations in carcinogenesis, as well as continuing to investigate ALK function in the fruitfly.

Luis Paz-Ares

Dr. Paz-Ares is currently Chair of the Oncology Department at the Hospital Universitario Virgen del Rocío, Vice-Director of the Instituto de Biomedicina de Sevilla (IBIS), and Associate Professor at the Seville University, in Seville, Spain.

He obtained his medical degree in 1986 from the Universidad Autonoma, where he also completed his studies for a PhD in Oncological Medicine in 1993. In 1995, he obtained his MSc in Clinical Pharmacology from the University of Glasgow, UK, and, in 2003, he was awarded a Master's degree in Clinical Units Management from the Universidad UNED in Madrid.

Dr. Paz-Ares originally trained in Medical Oncology and, in 1993, he took up a post as a European Society for Medical Oncology (ESMO) Fellow in New Drug Development at the CRC Department of Medical Oncology in Glasgow, UK. In 1995, he moved to the Doce de Octubre University Hospital in Madrid and was Head of the Lung and GU (genitourinary) Tumours and Drug Development Units. In 2007 he moved to his current position in Seville.

His main research interests include testing and developing novel therapies, particularly in lung and GU tumours. He is the author of more than 150 papers in peer-reviewed journals, as well as many book chapters. He is also an active member of various scientific societies (including the American Society of Clinical Oncology and ESMO) and collaborative groups (European Organisation for Research and Treatment of Cancer [EORTC]), the Spanish Lung Cancer Group, and the International Germ Cell Cancer Collaborative Group.

Solange Peters

Solange Peters, MD-PhD, PD-MER, is in charge of the thoracic malignancies program in the Department of Oncology of the University of Lausanne, and active in building a translational program in collaboration with the molecular oncology laboratory directed by Prof. D. Hanahan and Prof. E. Meylan as well as the Ludwig Institute. She has been trained in medical oncology and molecular biology in Switzerland and Italy. Her main field of interest is NSCLC new biomarker discovery and validation in preclinical and clinical settings. She is also heavily involved and interested in developing multimodality trials for locally advanced NSCLC. In the neighborhood of Ludwig Institute, and in collaboration with the technical institute (EPFL) she is involved in the development of promising new immunological approaches for the treatment of thoracic malignancies.

She is co-chair of the Swiss lung cancer research group (SAKK), and Scientific Coordinator as well as Chair of the Informatics Committee of the European Thoracic Oncology Platform (ETOP), responsible for communication, trial organization, coordination and related databases since 2012. She is a member and active in educational programs within ESMO and IASLC, and has been an ESMO Faculty member since 2012 and has been elected Executive board Member since 2014. She is also a member of the ESMO E-Learning and CME Working Group (ECWG). She has been elected the Swiss national representative of ESMO in 2013. She is IASLC publication committee member. She recently was elected in the IASLC Board of Directors 2013-2917. She is member of AACR and EORTC. She is the president of the Swiss education organization Forome, dedicated to cancer multidisciplinary professionals.

She was associate editor of Lung Cancer from 2011 to 2012 and became the Deputy Editor of the Journal of Thoracic Oncology (JTO) in 2013. She also acts as editor in chief of Cancer Treatment Communications and co-editor in chief of Journal of Oncopathology, as well as associate editor for Frontiers in Pharmacology of Anti-Cancer Drugs and in Thoracic Oncology, and a reviewer for several lung cancer and oncology journals.

Robert Pirker

Robert Pirker is currently Professor of Medicine and Program Director for Lung Cancer at the Department of Medicine I, Medical University of Vienna, Austria. He obtained a master's degree in Biochemistry in 1978 and his medical degree in 1979 from the University of Vienna. Robert Pirker trained in Internal Medicine, Hemato-Oncology and Nuclear Medicine at the University of Vienna. He also worked as NIH Visiting Fellow at the Laboratory of Molecular Biology (Chief: Dr. Ira Pastan), National Cancer Institute, Bethesda, MD, USA (1983-86).

He specialises in Hemato-Oncology. His research focuses on drug resistance mechanisms in patients with cancer, chemotherapy and targeted therapy of lung cancer, predictive factors in lung cancer, and anaemia management in patients with cancer. As a member of the IALT-Bio and LACE-Bio groups, he has been involved in the characterization of predictive factors with regard to adjuvant chemotherapy in patients with completely resected NSCLC. He was also the world-wide Co-ordinating Investigator of the FLEX trial.

Robert Pirker has published more than 150 articles, reviews or book chapters. He is an Editorial Board Member of *Lung Cancer,* ESMO Faculty Member on Chest Tumors, and has been a member including chair of the IASLC Education Committee. He was Congress President of the 8th Central European Lung Cancer Congress in 2002 and Chair of the Scientific Committee of the European Multidisciplinary Conference on Thoracic Oncology in 2009. He will be Congress President of the 14th Central European Lung Cancer Congress in 2014 and the 17th World Conference on Lung Cancer in 2016 in Vienna, Austria. He is also Chair of the Steering Committee of the recently launched Central European Initiative against Lung Cancer. Robert Pirker has received several scientific awards and has been a member of ESMO, ASCO and other scientific societies for many years.

David Planchard

Planchard David did his medical school in Paris, and a fellowship in medical Pneumo-oncology in Poitiers and Paris (France). He got his medical degree on october 2003 (pneumologist) and a Oncology degree on November 2004.

He joined Gustave-Roussy translational team on November 2006. He got a PhD in cellular molecular in 2009. He was visiting assistant professor in the department of molecular oncology, Quebec University in 2002. He is currently associate professor at Gustave-Roussy.

He is still works in the INSERM Unit U981 directed by Dr F. André (Thoracic Unit directed by Pr JC.Soria), a research lab where 30 people are working on the development of molecular predictors and new target identification. He is leading clinical trials in lung cancer in the department of thoracic oncology with Dr T. Le Chevalier, Dr B. Besse and Pr JC. Soria.

His input allowed thoracic tumor group to build a long term clinical research strategy based on molecular screening. He is leading a lung clinical trial addressing the efficacy of upfront genomic analysis (and high throughput technologies) to drive patients into specific targeted agents.

He is also responsible of developing the mesothelioma and thoracic neuroendocrine tumor research at Gustave-Roussy.

Martin Reck

Dr Martin Reck underwent medical training at the University of 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, Grosshansdorf. 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.

Dr 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 with targeted therapies.

Dr Reck is head of the department of Thoracic Oncology as well as head of the Clinical Trial Department in the Department of Thoracic Oncology at Hospital Grosshansdorf.

Dr Reck is 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, the European Thoracic Oncology Platform, the European Society of Medical Oncology and the American Society of Clinical Oncology.

David Rimm

Dr. David Rimm is a Professor in the Department of Pathology at the Yale University School of Medicine.

He completed an MD-PhD at Johns Hopkins University Medical School followed by a Pathology Residency at Yale and a Cytopathology Fellowship at the Medical College of Virginia.

Dr. Rimm is the Director of Translational Pathology and the Director of Yale Pathology Tissue Services.

His lab group (15 researchers) focuses on quantitative pathology using the AQUA® technology invented in his lab with projects related to predicting response to therapy in breast and lung cancer and predicting recurrence or metastasis in melanoma and lung cancer.

The technology has also been used in a series of efforts related to biospecimen science. He also has a group working on primary tumor culture using the conditionally reprogrammed cell method.

He is a member of a number of correlative science committees for multi-institutional breast cancer clinical trials including SWOG, ALLTO, and TEACH.

He also serves on the Molecular Oncology committee for the College of American Pathologists (CAP). He is currently supported by grants from both public and private sources.

He is an author of over 275 peer-reviewed papers and 8 patents and was a scientific co-founder of HistoRx, a digital pathology company (sold to Genoptix in 2012) and Metamark Genetics, a prognostic determinant company.

Giorgio Scagliotti

Dr. Scagliotti is currently Professor of Oncology at the University of Torino. Dr. Scagliotti earned his medical degree and completed the postgraduate training in Respiratory Medicine, Internal Medicine, and Medical Oncology at the University of Torino. He is currently chief of the Medical Oncology Division at the S. Luigi Hospital, Orbassano (Torino), Head of the Department of Oncology at University of Torino. From December 2007 to February 2012 he has been the Chairperson of the Postgraduate School in Respiratory Medicine. Over the last 15 years Dr. Scagliotti's research interests included experimental studies on basic and clinical applied research on lung cancer, including translational research. He has been the study coordinator of several European and international clinical trials on lung cancer chemotherapy and targeted therapies. He has been a key investigator in several Italian studies investigating the role of chemotherapy in early stage non-small cell lung cancer.

Dr. Scagliotti is a member of numerous scientific societies, including the Italian Society of Respiratory Medicine, the European Respiratory Society, the American Society of Clinical Oncology and the International Association for the Study of Lung Cancer. From 2002 to 2005 he was member of the International Affair Committee of the American Society of Clinical Oncology and from 2003-07 Executive Board member of the International Association for the Study of Lung Cancer. He served on the Publication Committee (2005-08) and in Program Committee of the American Society of Clinical Oncology in the period 2005-07. He is Associate Editor for Journal of Thoracic Oncology and International Editor for Clinical Lung Cancer. He is the author or co-author of more than 250 publications in peer-reviewed journals and he is the International Editor of the 4th Edition of "Lung Cancer : Principles and practice"

Rolf Stahel

Rolf A. Stahel, M.D. is head of the Center for Lung and Thoracic Oncology and Senior Staff Physician at the Clinic of Oncology, University Hospital of Zürich as well as Titular Professor of Medicine at the University of Zürich, Switzerland. He is certified in Internal Medicine and Medical Oncology by both the American and Swiss Board. His major interest is thoracic oncology, including multidisciplinary treatment approaches, translational research and targeted therapy.

He was a founding member and the first president of the Swiss Society for Medical Oncology. He served as president of the Swiss Institute for Applied Cancer Research from 1999 to 2005. He is member of the International Association for the Study of Lung Cancer (IASLC), where he served as chair of the fellowship committee and on the board of directors. In the European Society for Medical Oncology (ESMO) he served as National Representative from 1998 to 2004 and chaired Task Force on Guidelines from 1999 to 2005 and the educational committee from 2006 to 2011. He serves on the ESMO executive board since 2003 and is president of ESMO 2014 to 2015.

Since 2008 he is president of the foundation council of the International Breast Cancer Study Group (IBCSG). Since 2009 he is president of the European Thoracic Oncology Platform (ETOP), a foundation with the aim to bring together European collaborative groups and institutions focusing on research on thoracic malignancies.

He is editor in-chief of Lung Cancer and editor of Cancer Treatment Review and Progress on Tumor Research.

Kostas Syrigos

Professor Kostas Syrigos graduated from Athens School of Medicine in 1988. He was trained in Internal Medicine at the Laikon University Hospital (Athens University) and in Medical Oncology at the Hammersmith Hospital (Imperial College of Medicine, Sciences & Art, London University). He got his MD thesis with distinction from the Athens School of Medicine, in 1995 and his PhD thesis from the Imperial College of Science, Technology and Medicine, London University, in 2000. He worked as Medical Oncologist Senior Registrar at the Hammersmith and St Bartholomew's Hospitals, in London and as consultant at the Sotiria General Hospital, in Athens. In 2002 he was appointed Assc. Professor of Oncology in Medicine and Head of the Sotiria Oncology Unit. From 2006 he is also Visiting Professor of Thoracic Oncology at Yale University, CT, USA. His main fields of interest are Targeted Therapies, drugs development as well as Thoracic and Head & Neck oncology.

Dr Syrigos participated in several international clinical trials Phase I-IV in lung, colon, head & neck and pancreatic cancer. He is a member of numerous scientific societies, including the European Society of Medical Oncology (ESMO), the European Respiratory Society (ERS), the American Society of Clinical Oncology (ASCO), the American Association of Cancer Research (AACR) and the International Association for the Study of Lung Cancer (IASLC). He is a manuscript reviewer for 18 scientific journals and currently serves on the editorial board of 5 scientific journals. He is the editor of 8 International Scientific Volumes. He has contributed 80 chapters in international books and he is the author of 350 peer-reviewed, international articles, with more than 5.000 citations. He is currently sitting as member of the ESMO Translational Research Group and of the MASCC Board of Directors.

Johan Vansteenkiste

Professor Johan 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.

Professor Vansteenkiste studied Medicine at the Catholic 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 Catholic University of Leuven in 1996.

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

He is the principal investigator or co-investigator in several clinical trials in the area of lung cancer. He is Associate Editor at the Journal of Thoracic Oncology, member of the editorial board of the Journal of Clinical Oncology and several other journals, and author or co-author of more than 200 peer-reviewed papers and book chapters on Respiratory Oncology.

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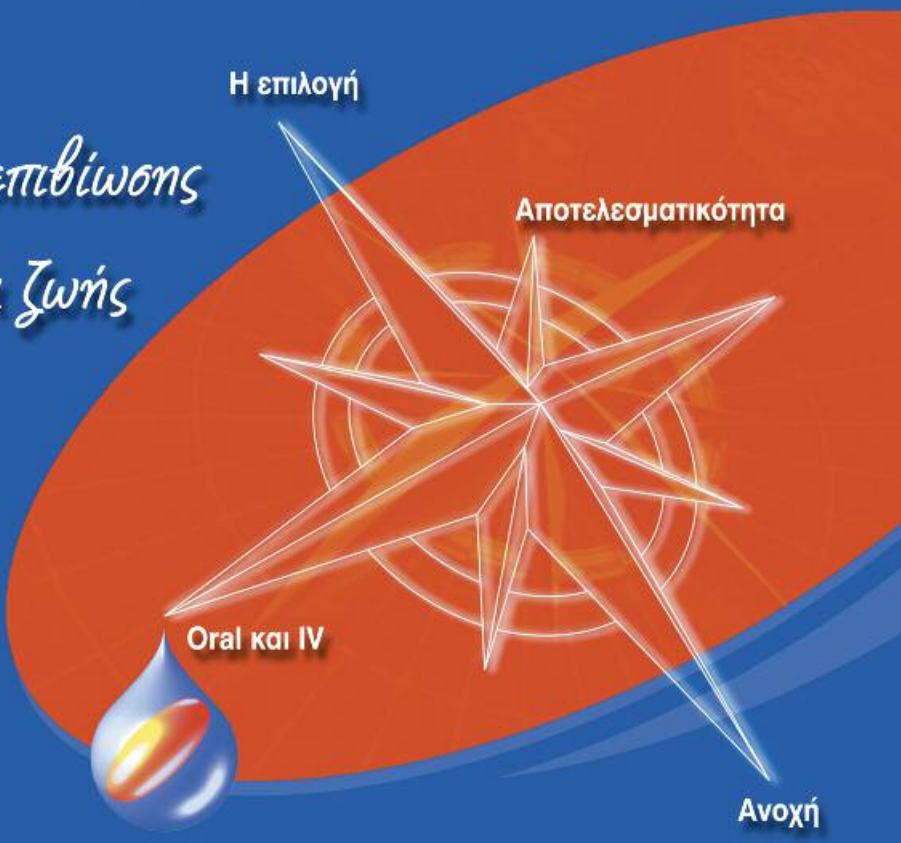

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1. Sasaki T, et al. Eur J Cancer. 2010;46:1773–80.

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XALKORI (crizotinib)

ΣΚΛΗΡΟ ΚΑΨΑΚΙΟ 200 mg και 250 mg

ΘΕΡΑΠΕΥΤΙΚΕΣ ΕΝΔΕΙΞΕΙΣ: Το XALKORI ενδείκνυται για τη θεραπεία ενηλίκων με ήδη υποβληθέντα σε θεραπεία θετικό στην κινάση του αναπλαστικού λεμφώματος (ALK) προχωρημένο μη μικροκυτταρικό καρκίνο του πνεύμονα (NSCLC-Non-Small Cell Lung Cancer). **ΔΟΣΟΛΟΓΙΑ ΚΑΙ ΤΡΟΠΟΣ ΧΟΡΗΓΗΣΗΣ:** **Για λεπτομερείς οδηγίες δοσολογίας, συμβουλευτείτε την πλήρη Περίληψη Χαρακτηριστικών του Προϊόντος.** Η έναρξη και η παρακολούθηση της θεραπείας με XALKORI πρέπει να γίνεται από γιατρό με εμπειρία στη χρήση αντικαρκινικών φαρμακευτικών προϊόντων. **ΑΝΤΕΝΔΕΙΞΕΙΣ:** Υπερευαισθησία στο crizotinib ή σε κάποιο από τα έκδοχα. Σοβαρή ηπατική δυσλειτουργία. **ΕΙΔΙΚΕΣ ΠΡΟΕΙΔΟΠΟΙΗΣΕΙΣ ΚΑΙ ΠΡΟΦΥΛΑΞΕΙΣ ΚΑΤΑ ΤΗ ΧΡΗΣΗ:** Ηπατοτοξικότητα: Υπήρξε επαγόμενη από φάρμακο ηπατοτοξικότητα με θανατηφόρα έκβαση. Οι περιπτώσεις αυτές έχουν εμφανισθεί κατά τη διάρκεια της θεραπείας με XALKORI σε λιγότερο από 1% των ασθενών σε κλινικές δοκιμές. Έχουν παρατηρηθεί ταυτόχρονες αυξήσεις στην ALT μεγαλύτερες από 3 x ULN και στην ολική χολερυθρίνη μεγαλύτερες από 2 x ULN χωρίς αυξημένη αλκαλική φωσφατάση σε λιγότερο από 1% των ασθενών σε κλινικές δοκιμές. Αυξήσεις σε Βαθμό 3 ή 4 σε αυξημένες τιμές της ALT παρατηρήθηκαν στο 6% των ασθενών στη Μελέτη Α και στο 8% των ασθενών στη Μελέτη Β. Οι αυξήσεις Βαθμού 3 και 4 ήταν γενικά ασυμπτωματικές και αναστρέψιμες μετά τη διακοπή της δόσης. Οι ασθενείς συνήθως συνέχιζαν τη θεραπεία σε χαμηλότερη δόση χωρίς υποτροπή. Ωστόσο, σε 1 ασθενή από τη Μελέτη Α (<1%) και σε 3 ασθενείς από τη Μελέτη Β (1%) χρειάστηκε οριστική διακοπή της θεραπείας. Οι αυξήσεις των τρανσαμινασών εμφανίστηκαν γενικά κατά τη διάρκεια των 2 πρώτων μηνών της θεραπείας. Δε θα πρέπει να χρησιμοποιείται το XALKORI σε ασθενείς με σοβαρή ηπατική δυσλειτουργία. Θα πρέπει να γίνεται παρακολούθηση των εξετάσεων της ηπατικής λειτουργίας συμπεριλαμβανομένων των ALT, AST και ολικής χολερυθρίνης δύο φορές τον μήνα κατά τη διάρκεια των 2 πρώτων μηνών της θεραπείας, στη συνέχεια μια φορά το μήνα και όπως ενδείκνυται κλινικώς, με συχνότερα επαναλαμβανόμενες εξετάσεις για αύξηση Βαθμών 2, 3 ή 4. Πνευμονίτιδα: Σε κλινικές δοκιμές, το XALKORI έχει συσχετισθεί με σοβαρή, απειλητική για τη ζωή, ή θανατηφόρα πνευμονίτιδα που σχετίζεται με τη θεραπεία, με συχνότητα 4 στους 386 (1%) ασθενείς στις Μελέτες Α και Β. Όλες αυτές οι περιπτώσεις εμφανίστηκαν μέσα σε διάστημα 2 μηνών από την έναρξη της θεραπείας. Οι ασθενείς με πνευμονολογικά συμπτώματα ενδεικτικά πνευμονίτιδας θα πρέπει να παρακολουθούνται. Θα πρέπει να γίνεται προσωρινή διακοπή της θεραπείας με XALKORI εάν υπάρχει υποψία πνευμονίτιδας. Θα πρέπει να αποκλείονται άλλες αιτίες πνευμονίτιδας και να διακόπτεται οριστικά το XALKORI σε ασθενείς με διάγνωση πνευμονίτιδας σχετιζόμενης με τη θεραπεία. Παράταση διαστήματος QT: Έχει παρατηρηθεί παράταση του διαστήματος QTc, η οποία μπορεί να οδηγήσει σε αυξημένο κίνδυνο για κοιλιακές ταχυαρρυθμίες (πχ., κοιλιακή ταχυκαρδία δίκην ριπιδίου) ή αιφνίδιο θάνατο. Ο κίνδυνος παράτασης του διαστήματος QTc μπορεί να αυξηθεί σε ασθενείς που λαμβάνουν ταυτόχρονα αντιαρρυθμικά και σε ασθενείς με σχετική προϋπάρχουσα καρδιακή νόσο, βραδυκαρδία, ή ηλεκτρολυτικές διαταραχές (πχ., λόγω διάρροιας ή εμετού). Το XALKORI θα πρέπει να χορηγείται με προσοχή σε ασθενείς με ιστορικό ή προδιάθεση για παράταση του διαστήματος QTc ή σε ασθενείς οι οποίοι λαμβάνουν φαρμακευτικά προϊόντα που είναι γνωστό ότι παρατείνουν το διάστημα QT. Κατά τη χρήση του XALKORI σε αυτούς τους ασθενείς, θα πρέπει να λαμβάνεται υπόψη περιοδική παρακολούθηση μέσω ηλεκτροκαρδιογραφημάτων και μέτρησης των ηλεκτρολυτών. Επιδράσεις στην όραση: Οπτική διαταραχή εμφανίσθηκε σε ασθενείς στη Μελέτη Α και Μελέτη Β. Θα πρέπει να εξετασθεί το ενδεχόμενο οφθαλμολογικής αξιολόγησης αν η οπτική διαταραχή εμμένει ή επιδεινώνεται σε βαρύτητα. Αλληλεπιδράσεις μεταξύ των φαρμάκων: Θα πρέπει να αποφεύγεται η συγχορήγηση του crizotinib με ισχυρούς αναστολείς/επαγωγείς του CYP3A4 και με υποστρώματα του CYP3A4 με στενό θεραπευτικό δείκτη. Ηλικιωμένοι: Περιορισμένες πληροφορίες είναι διαθέσιμες για ασθενείς ηλικίας ≥65 ετών και δεν υπάρχει καμία πληροφορία για ασθενείς ηλικίας μεγαλύτερης των 85 ετών. Ιστολογία μη-αδενοκαρκινώματος: Περιορισμένες πληροφορίες είναι διαθέσιμες για ασθενείς με ALK-θετικό NSCLC με ιστολογία μη-αδενοκαρκινώματος. Το κλινικό όφελος μπορεί να είναι χαμηλότερο σε αυτόν τον υποπληθυσμό, το οποίο θα πρέπει να λαμβάνεται υπόψη πριν τη λήψη εξατομικευμένων θεραπευτικών αποφάσεων. **ΑΝΕΠΙΘΥΜΗΤΕΣ ΕΝΕΡΓΕΙΕΣ:** Τα δεδομένα που περιγράφονται παρακάτω αντανακλούν την έκθεση στο XALKORI 386 ασθενών με ALK-θετικό NSCLC, με προηγούμενη θεραπευτική αντιμετώπιση, οι οποίοι συμμετείχαν σε 2 κλινικές δοκιμές μονού σκέλους (Μελέτες Α και Β). Αυτοί οι ασθενείς έλαβαν αρχική δόση 250 mg χορηγούμενη από το στόμα δύο φορές την ημέρα, συνεχώς. Συγκριτικά δεδομένα ασφαλείας από τυχαιοποιημένες κλινικές δοκιμές δεν είναι ακόμη διαθέσιμα. Παρατίθενται οι συχνότητες εμφάνισης των ανεπιθύμητων ενεργειών που αναφέρθηκαν συχνά σε ασθενείς που έλαβαν XALKORI. Οι περισσότερες ανεπιθύμητες ενέργειες ήταν Βαθμού 1 ή 2 σε βαρύτητα. Οι πιο συχνές ανεπιθύμητες ενέργειες οποιουδήποτε βαθμού (>20%) και στις δύο μελέτες ήταν οπτική διαταραχή, ναυτία, διάρροια, έμετος, οίδημα, δυσκοιλιότητα και κόπωση. Οι πιο συχνές ανεπιθύμητες ενέργειες Βαθμού 3 ή 4 (≥ 3%) και στις δύο μελέτες ήταν αυξημένη ALT και ουδετεροπενία. Μειώσεις της δόσης που σχετίζονται με ανεπιθύμητες ενέργειες έγιναν στο 6% των ασθενών στη Μελέτη Α και στο 15% των ασθενών στη Μελέτη Β. Η συχνότητα των σχετιζόμενων με τη θεραπεία ανεπιθύμητων ενεργειών που οδήγησαν στην οριστική διακοπή της θεραπείας ήταν 2% στη Μελέτη Α και 4% στη Μελέτη Β.

Πολύ συχνές (≥ 1/10): Ουδετεροπενία, μειωμένη όρεξη, νευροπάθεια[α], ζάλη, δυσγευσία, οπτική διαταραχή[γ], έμετος, ναυτία, διάρροια, δυσκοιλιότητα, κόπωση[γ], οίδημα[α], αμινοτρανσφεράση της αλανίνης αυξημένη **Συχνές (≥ 1/100 έως < 1/10):** Λευκοπενία, λεμφοπενία, αναιμία, υποφωσφαταιμία, βραδυκαρδία[α], πνευμονίτιδα, διαταραχή σχετιζόμενη με τον οισοφάγο[α], δυσπεψία, εξάνθημα, ηλεκτροκαρδιογράφημα, διάστημα QT παρατεταμένο, ασπαρτική αμινοτρανσφεράση αυξημένη, αλκαλική φωσφατάση αίματος αυξημένη **Όχι συχνές (≥ 1/1.000 έως < 1/100):** Κύστη νεφρού[β γ] Περιλαμβάνει περιπτώσεις που αναφέρθηκαν εντός των ομαδοποιημένων όρων: οίδημα (οίδημα, οίδημα περιφερικό), διαταραχή σχετιζόμενη με τον οισοφάγο (γαστροοισοφαγική παλινδρόμηση, οδυνοφαγία, άλγος του οισοφάγου, έλκος του οισοφάγου, οισοφαγίτιδα, οισοφαγίτιδα από παλινδρόμηση, δυσφαγία, επιγαστρική δυσφορία), νευροπάθεια (νευραλγία, περιφερική νευροπάθεια, παραισθησία, περιφερική κινητική νευροπάθεια, περιφερική αισθητικοκινητική νευροπάθεια, διαταραχή αισθητικότητας), οπτική διαταραχή (διπλωπία, φωτοψία, όραση θαμπή, οπτική δυσλειτουργία, εξιδρώματα του υαλοειδούς σώματος), βραδυκαρδία (βραδυκαρδία, φλεβοκομβική βραδυκαρδία) και κόπωση (εξασθένιση, κόπωση)

[α] Περιλαμβάνει 1 ανεπιθύμητη ενέργεια Βαθμού 5 [β] Περιλαμβάνει σύνθετες κύστεις των νεφρών

Ηπατοτοξικότητα: Υπήρξε επαγόμενη από φάρμακα ηπατοτοξικότητα με θανατηφόρα έκβαση. Οι περιπτώσεις αυτές έχουν εμφανισθεί σε κλινικές δοκιμές κατά τη διάρκεια της θεραπείας με XALKORI σε λιγότερο από 1% των ασθενών. Έχουν παρατηρηθεί ταυτόχρονες αυξήσεις στην ALT μεγαλύτερες από 3 x ULN και στην ολική χολερυθρίνη μεγαλύτερες από 2 x ULN χωρίς αυξημένη αλκαλική φωσφατάση σε λιγότερο από 1% των ασθενών σε κλινικές δοκιμές. Αυξήσεις σε Βαθμό 3 ή 4 σε αυξημένες τιμές της ALT παρατηρήθηκαν στο 6% των ασθενών στη Μελέτη Α και στο 8% των ασθενών στη Μελέτη Β. Οι αυξήσεις Βαθμού 3 και 4 ήταν γενικά ασυμπτωματικές και αναστρέψιμες μετά τη διακοπή της δόσης. Οι ασθενείς συνήθως συνέχιζαν τη θεραπεία σε χαμηλότερη δόση χωρίς υποτροπή. Ωστόσο, σε 1 ασθενή από τη Μελέτη Α (<1%) και σε 3 ασθενείς από τη Μελέτη Β (1%) χρειάστηκε οριστική διακοπή της θεραπείας. Οι αυξήσεις των τρανσαμινασών εμφανίστηκαν γενικά κατά τη διάρκεια των 2 πρώτων μηνών της θεραπείας. Δε θα πρέπει να χρησιμοποιείται το XALKORI σε ασθενείς με σοβαρή ηπατική δυσλειτουργία. Θα πρέπει να γίνεται παρακολούθηση των εξετάσεων ηπατικής λειτουργίας συμπεριλαμβανομένων των ALT, AST και ολικής χολερυθρίνης δύο φορές τον μήνα κατά τη διάρκεια των 2 πρώτων μηνών της θεραπείας, στη συνέχεια μια φορά το μήνα και όπως ενδείκνυται κλινικώς, με πιο συχνές επαναλαμβανόμενες εξετάσεις για αύξηση Βαθμών 2, 3 ή 4. *Επιδράσεις στην όραση:* Οπτική διαταραχή, που περιλαμβάνει διπλωπία, φωτοψία, θαμπή όραση, οπτική δυσλειτουργία και εξιδρώματα του υαλοειδούς σώματος, εμφανίστηκαν σε 76 (61%) ασθενείς στη Μελέτη Α και σε 149 (57%) ασθενείς στη Μελέτη Β. Το σύμβαμα αυτό αναφέρθηκε ως ήπιο (96%), μέτριο (3%) και σοβαρό (<1%) με διάμεσο χρόνο έως την εμφάνισή του 15 και 6 ημέρες στις Μελέτες Α και Β, αντίστοιχα. Σε κανέναν από τους ασθενείς που συμμετείχαν στις Μελέτες Α και Β δεν απαιτήθηκε μείωση της δόσης ή οριστική διακοπή της θεραπείας με crizotinib λόγω οπτικής διαταραχής. Ωστόσο, σε 1 ασθενή στη Μελέτη Α και σε 3 ασθενείς στη μελέτη Β έγινε προσωρινή διακοπή της θεραπείας. Θα πρέπει να εξετασθεί το ενδεχόμενο οφθαλμολογικής αξιολόγησης αν η οπτική διαταραχή εμμένει ή επιδεινώνεται σε βαρύτητα. *Διαταραχές του γαστρεντερικού συστήματος:* Ναυτία, διάρροια, έμετος και δυσκοιλιότητα ήταν οι πιο συχνά αναφερόμενες γαστρεντερικές διαταραχές και ήταν κυρίως βαρύτητας Βαθμού 1. Η υποστηρικτική φροντίδα για τις γαστρεντερικές διαταραχές μπορεί να περιλαμβάνει τη χορήγηση καθιερωμένων αντιεμετικών ή/και αντιδιαρροϊκών ή καθαρτικών φαρμακευτικών προϊόντων. *Διαταραχές του νευρικού συστήματος:* Νευροπάθεια,κυρίως περιφερική νευροπάθεια, εμφανίστηκαν σε 11 (9%) ασθενείς στη Μελέτη Α και σε 33 (13%) ασθενείς στη Μελέτη Β και ήταν κυρίως βαρύτητας Βαθμού 1. Ζάλη και δυσγευσία αναφέρθηκαν επίσης πολύ συχνά σε αυτές τις μελέτες, αλλά ήταν όλες Βαθμού 1 ή 2 σε βαρύτητα. *Εργαστηριακές ανωμαλίες/εξετάσεις - Αύξηση των τρανσαμινασών:* Αυξήσεις σε Βαθμό 3 ή 4 της ALT παρατηρήθηκε στο 6% των ασθενών στη Μελέτη Α και στο 8% των ασθενών στη Μελέτη Β. Οι αυξήσεις Βαθμού 3 και 4 ήταν σε γενικές γραμμές ασυμπτωματικές και αναστρέψιμες με τη διακοπή της χορήγησης. Συνήθως, η θεραπεία επαναχορηγήθηκε στους ασθενείς σε μειωμένη δόση χωρίς υποτροπή. Ωστόσο, απαιτήθηκε οριστική διακοπή της θεραπείας σε 1 ασθενή από τη Μελέτη Α (<1%) και σε 3 ασθενείς της Μελέτης Β (1%). Ταυτόχρονες αυξήσεις της ALT >3 x ULN και της ολικής χολερυθρίνης >2 x ULN χωρίς αυξημένη αλκαλική φωσφατάση εντοπίστηκαν σε 1 από τους 375 (<0,5%) ασθενείς με διαθέσιμα εργαστηριακά δεδομένα και στις δύο μελέτες. Θα πρέπει να γίνεται παρακολούθηση των εξετάσεων ηπατικής λειτουργίας, συμπεριλαμβανομένων των ALT, AST και ολικής χολερυθρίνης δύο φορές τον μήνα κατά τη διάρκεια των 2 πρώτων μηνών της θεραπείας, στη συνέχεια μια φορά το μήνα σύμφωνα με τις κλινικές ενδείξεις, με συχνότερους επαναληπτικούς ελέγχους για τις αυξήσεις Βαθμού 2, 3 ή 4. *Αιματολογικές εργαστηριακές ανωμαλίες:* Στη Μελέτη Α, παρατηρήθηκαν στους ασθενείς μειώσεις των λευκοκυττάρων και αιμοπεταλίων Βαθμού 3 ή 4 σε συχνότητα <3% έκαστη, καθώς και μειώσεις των ουδετερόφιλων και λεμφοκυττάρων Βαθμού 3 ή 4 σε συχνότητα 10% και 14%, αντίστοιχα. Στη Μελέτη Β, παρατηρήθηκαν στους ασθενείς μειώσεις των λευκοκυττάρων Βαθμού 3 ή 4 σε συχνότητα 3%, μειώσεις των ουδετερόφιλων Βαθμού 3 ή 4 σε συχνότητα 9%, μειώσεις των λεμφοκυττάρων Βαθμού 3 ή 4 σε συχνότητα 14% και μειώσεις των αιμοπεταλίων Βαθμού 3 ή 4 σε συχνότητα <1%. Ο πλήρης αιματολογικός έλεγχος συμπεριλαμβανομένων διαφοροποιημένων επιπέδων λευκοκυττάρων πρέπει να παρακολουθείται ανάλογα με τις κλινικές ενδείξεις, με συχνότερους επαναληπτικούς ελέγχους αν εντοπιστούν παθολογικά ευρήματα Βαθμού 3 ή 4 ή αν εμφανιστεί πυρετός ή λοίμωξη. Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών Η αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους-κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες του τομέα της υγειονομικής περίθαλψης να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες μέσω: **Ελλάδα** Εθνικός Οργανισμός Φαρμάκων, Μεσογείων 284, GR-15562 Χολαργός, Αθήνα, Τηλ: + 30 21 32040380/337, Φαξ: + 30 21 06549585, Ιστότοπος: http://www.eof.gr **Κύπρος** Φαρμακευτικές Υπηρεσίες, Υπουργείο Υγείας, CY-1475 Λευκωσία, Φαξ: + 357 22608649, Ιστότοπος: www.moh.gov.cy/phs.

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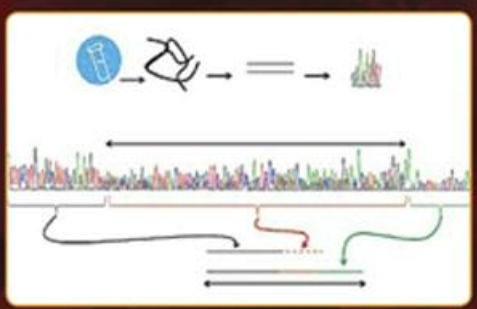

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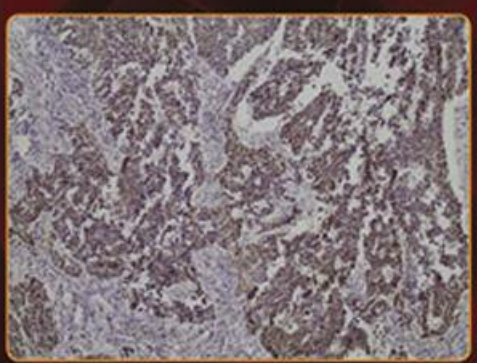

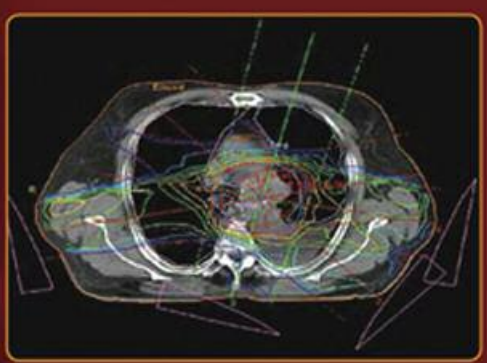

Abstracts

FRIDAY, January 31st 2014

Saturday, February 1st 2014

Molecular biology of lung cancer

Personalized treatment on lung cancer patients

OPTIMAL TISSUE ACQUISITION AND MINIMAL REQUIREMENTS

by Keith Kerr

Optimal tissue acquisition

The purpose of acquiring tissue from a patient with lung cancer is to secure a tissue diagnosis of malignancy, allow subtyping of the tumour and support biomarker testing so that the best therapy may be offered to the patient. The handling of tissue samples after removal, during transport to the pathology laboratory and during processing and examination in pathology is crucially important. Technical mistakes can lead to diagnostic errors and false biomarker test results.

In a patient with limited stage disease, who will have surgical tumour resection with curative intent, there is less pressure to provide a complete range of diagnostic information, since the tumour, when resected, will provide more material for full diagnosis. However, this is rarely an advantage to the pathologist since the likely respectability of the tumour is often not known at initial diagnosis. It is better for the pathologist to assume that the sample they have is all they will have to work with.

Most pathology investigations in lung cancer concern patients with advanced disease. There is a wide range of possible sample types that may be provided for diagnosis; various approaches to the primary tumour or access to metastatic disease. General principles that apply include; least problematic for the patient, accessibility, likely yield of material, sampling highest stage disease, diagnosis and staging from one sample, or one biopsy session/procedure.

Different sampling approaches generally differ in the likely yield of diagnostic material. This is a function of the access achievable; the instruments used for sampling and whether or not the sample is taken 'blind', or with targeted imaging guidance, or by direct visualization during, for example, an open surgical procedure. Most samples are relatively challenging to obtain and are relatively small. Success in biopsy procedures was previously measured by how often a malignant diagnosis was secured. Nowadays this is an inadequate measure since the treating oncologist requires more than a simple statement of 'malignant'; they need tumour subtype as specific as possible and appropriate biomarker data. This extra information requires more tissue to work with.

Debates regarding cytology versus biopsy are overemphasised and exaggerated, depending on bias and prejudice. Cytology samples may be better than biopsy samples for some biomarker tests since DNA may be better preserved; biopsy samples may be better due to higher average tumour yield and consistent compatibility with immunohistochemistry (IHC). Such is the range of cytology and biopsy type samples, however, that such generalizations are actually quite unhelpful. Some cytology type samples can provide large amounts of tumour, others only minimal samples. The same applies to biopsy samples. No particular sampling approach has 'magic properties, guaranteeing diagnostic success'. The outcome of the procedure in terms of tumour yield is just as dependent upon the skill, patience and tenacity of the operator as it is on the particular instruments in use.

Processing and handling are vitally important. In general, we have only one opportunity to receive, process/fix and prepare a tissue sample. Thus it must be done correctly and must be adequate for all the diagnostic procedures that may be required. It is accepted that certain ways of processing may favour certain types of pathological test but we do not have this flexibility in the majority of patients. The accepted and recommended standard for tissue biopsy samples is fixation in 10% neutral buffered formalin. Cytology samples have traditionally been exposed to a wider range of alcohol or other fixative types. These may preserve DNA better than formalin but can be problematic for IHC. Cytology cell material is increasingly 'post-fixed' in formalin, for the preparation of cytology cell blocks. This is recommended to facilitate biomarker testing in cytology samples in most circumstances.

Various approaches are recommended for limiting the cutting of blocks and use of tissue, to prevent waste and allow a wider range of testing without exhausting the material available.

For immunohistochemical testing, it is important that laboratories optimise their techniques to suit the normal or average processing of samples in that laboratory. If laboratories receive processed tissue blocks from other laboratories for biomarker testing, test variability may be encountered. For in situ hybridization, many of these same principles will apply. Caution must be exercised if sections used for these techniques have been pre-cut and stored for a period before usage. Antigen

and nucleic acid integrity deteriorate with storage. It is much better to use freshly cut sections. The same principles apply to DNA integrity for the purposes of mutation testing. In addition, prolonged fixation increases DNA damage (cross-linking) so fixation should be limited to between 6 and 48 hours where possible. Long periods of fixation may render mutation testing difficult or impossible.

Minimal requirements

The concept of a minimum requirement may appear a helpful guide but there is always the danger that 'minimum' becomes the *de facto* standard; this is usually bad practice.
For most biomarker testing there are actually few or no data to properly inform any answer to the perennial question posed to pathologists; 'How much do you need?' Furthermore, this question is largely irrelevant and possibly harmful, since the operator taking the sample usually has, with the possible exception of cytology sampling covered by on site cytopathology assessment (ROSE), little or no idea of how much actual tumour is present in the tissue sample being provided. The correct answer to this question is, in general, 'as much tissue/material as you can safely obtain'.
It is possible to read an IHC result, and theoretically possible to read a FISH test, on a single tumour cell, and single cell DNA PCR can be achieved in certain laboratory conditions. But what would any of those data actually mean? Tumour heterogeneity at a molecular level is a fact but we are largely ignorant of its clinical meaning and how to deal with it. In certain circumstances pathologists can make a diagnosis of carcinoma on a very small number of cells (<10), but reliable biomarker testing would require more.
For most IHC tests there are no rules, other than vague statements about the proportion of cells that should express a given marker for the test to be regarded as positive. In recognition of staining heterogeneity, however, some arbitrary limit may be set; for example, recommendations for reading MET IHC to select patients with NSCLC into trials of onartuzamab require >50 tumour cells to be assessed.
For FISH testing there are similar issues. Furthermore, given that in lung cancer, in situ hybridisation aims to detect a break apart signal (eg ALK) or signal amplification (eg FGFR1), with each discrete nuclear hybridisation 'point' occurring somewhere in a 3-dimensional nucleus, then tissue sectioning may truncate signals in individual nuclei. Thus, an ALK FISH test must allow assessment of at least 50 suitable nuclei.
For mutation testing the issues are rather different. For reasons already mentioned, as to how the sample reflects the tumour overall, extracting DNA from smaller numbers of tumour cells risks an unrepresentative result. More important, however, given the fact that most tumour samples comprise neoplastic and non-neoplastic cells, is the proportion of tumour cells in the sample used for DNA extraction. Mutant alleles will always to some extent, be diluted by wild type alleles, from the tumour cells but also from non-neoplastic tissue elements. Different mutation testing techniques have differing sensitivities for detecting mutant alleles at low frequency. Standard direct Sanger sequencing has a sensitivity of 10-20% depending on methods used and operator experience. Other methods have higher sensitivity. Very high sensitivity methods, however, risk false positive outcomes and the possibility of detecting clinically insignificant alterations. It is dangerous to rely exclusively upon very high sensitivity methodology to compensate for poor, low tumour content test samples. Efforts should be made to increase as much as possible the tumour cell % in samples for DNA extraction, to at least 20% and preferably >50%.
Optimal tissue collection and processing is vital to underpin accurate biomarker assessment. Failure to follow basic principles and guidelines poses a real risk of inaccurate or misleading results and potential harm to patients.

COORDINATING THE PATHOLOGY LAB WITH THE CLINICAL PRACTICE

by Niki Karachaliou

Lung cancer is the leading cause of cancer-related mortality, accounting for approximately 1.4 million deaths per year worldwide. During the past decade, scientific and technologic progress in cancer genomics research has accelerated the pace of discoveries that can be potentially trans-

lated into significant clinical advances for patients with lung cancer. Indeed, patients' lung cancers can clearly harbour a variety of 'druggable' mutant signaling proteins, even in tumours with similar-appearing histology. Thus, a need has emerged to have tumour genetics inform clinical care which allows for drugs to be prioritized for patients in the order of likely benefit, leading to improved outcomes with potentially less toxicity. For instance, activating EGFR mutations have been described in 10-26% of lung adenocarcinomas and sensitize tumours to the treatment with EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib and afatinib. The EML4-ALK rearrangement identifies a subset (3-7%) of tumours that can benefit from the treatment with crizotinib, while recently, ROS1 fusions, detected in 1.7% of adenocarcinomas, predict response also to crizotinib therapy. Furthermore, HER2 mutations have been described in 1.7%-6% of NSCLC, prevalently adenocarcinomas and never-smoker and these patients derive benefit from HER2 targeted treatment. The presence of HER2 mutations is not associated with the amplification of the gene and is mutually exclusive with EGFR mutations and ALK rearrangements. BRAF mutations have been identified in 2-3% of NSCLC, usually adenocarcinomas without concomitant EGFR, KRAS mutations or ALK fusion and a phase II trial demonstrated the efficacy of dabrafenib in BRAFV600E mutated NSCLC patients. In 1.2% of lung adenocarcinomas, RET rearrangements can be identified. These tumours may be targeted by clinically available drugs such as vandetanib, cabozantinib, ponatinib, sorafenib and sunitinib. Although PIK3CA mutations can be found in a minority (2%) of NSCLC, these tumours disappear when the expression of PIK3CA is down-regulated and tend to respond to the treatment with BEZ235 a dual PI3K and mTOR inhibitor. There are several PI3K and mTOR pathway inhibitors under evaluation in clinical trials, such as BKM120 and GDC-0941.

On the other hand, squamous cell carcinomas of the lung are characterized by an uneven FGFR1 gene copy number distribution. Fluorescence in situ hybridization assays need to address focality and heterogeneity of FGFR1 in these tumours. Therapeutic effects of FGFR1 tyrosine kinase inhibitors seem to be dependent on significantly increased FGFR1 gene copy numbers. Although it still needs to be clarified whether FGFR1 amplification serves as a surrogate marker for receptor protein overexpression, since the receptor itself represents obviously the therapeutic target, current clinical trials with FGFR1 inhibitors enroll patients who are found to be "FGFR1 amplified". For squamous lung cancer histology DDR2 mutations are another potential druggable target. This receptor tyrosine kinase has been described mutated in about 4% of squamous cell carcinoma and the combined treatment of dasatinib and erlotinib induced a partial response in a patient with a squamous cell lung cancer with DDR2 and without EGFR mutation.

The ongoing analyses of tumour oncogenic alterations performed using next generation sequencing will better identify the molecular aberrations of NSCLC and will help to classify these tumours. Nonetheless, the challenges of clinical tumour resistance, both intrinsic and acquired, remain a limiting bottleneck to meaningfully impact long term survival outcome in cancer patients undergoing effective genotype-matching targeted therapy. Following the tumour's clonal evolution in each patient and promptly prescribe the most effective treatment using circulating tumour cells or circulating cell-free tumour DNA are promising methods to repetitively analyze tumour DNA. However, there is a strong rationale for conducting serial tumour rebiopsies in oncogene driven lung cancer patients under targeted therapy especially during the early treatment time window, to interrogate the mechanism and potential targets driving the emergence of drug escape in the evolutionary process of tumour resistance development.

CLINICAL TRIALS ENDPOINT: OS VS PFS

by Jean-Yves Douillard

Overall survival improvement is the ultimate goal to be achieved from new therapeutic approaches in randomized clinical trials. The validity of a given trial endpoint however differs according to the stakeholder point of view: patients, clinicians, regulators or payers.

Overall survival has long been considered as the gold standard to be reached in a clinical trial. It is universally accepted as a direct, easy to measure and precise end-point

With the increasing number of drugs and lines of treatment in most of the tumor types, as well as cross-over whenever available, the impact of an experimental treatment in a clinical trial is more difficult to precisely analyze in terms of overall survival. In addition, overall survival needs a long follow-up to reach enough events, quite often requires a large sample size and also includes non-cancer related deaths.

For all the reasons above, surrogate end-points are sometimes used, like progression-free survival (PFS). It is sometimes accepted by regulatory agencies for approval in randomized trials. PFS includes Duration of Disease Control, PFS is not affected by cross-over, and requires a shorter follow-up than overall survival. PFS however has limitations including possible assessment biases, variable definitions among studies, requirement of repeated radiological assessments and is not always statistically validated as surrogate for overall survival and depends on tumor types.
In Non-Small Cell Lung Cancer treated with chemotherapy PFS and survival are rather short. The short survival time after progression implies that differences in overall survival are likely to be observed for truly effective new treatments. During the era of platinum-based doublet chemotherapy meta-analysis looked for a correlation between PFS and OS to possibly recommend PFS as a surrogate endpoint for OS. PFS showed some correlation with OS but was too weak to suggest that PFS could be a statistically acceptable surrogate endpoint for OS in patients with metastatic NSCLC. Although about two-thirds of the treatment effects on OS might have been attributable to the treatment effect on PFS, no clear correlation could be established with OS. The generally modest benefit obtained on PFS may explain the absence of a clear correlation with OS. Only new drugs showing a major PFS benefit would be expected to also have a significant benefit on OS.
The situation seems to be different with targeted agents. The use of EGFR TKI in EGFR mutant NSCLC in first line has demonstrated impressive median PFS and Hazard ratios for progression. None of the trials showed a benefit on OS. The explanation here relies in the use of cross-over treatment at progression and opens a new concept to define end-points for such trials. Statistical tests like the Inverse Probability of Censoring Weighted may in some cases be used to evaluate the impact of cross-over.
In conclusion, the choice of an end-point for a clinical trial should depend on the goal to be achieved by the trial. For registration purpose, OS is often preferred but in recent examples with targeted agents PFS has been accepted by regulatory agencies. For clinicians, OS is also the gold-standard, especially in lung cancer where only a limited number a treatment lines can be delivered. In other tumor type, an improved PFS on successive lines of treatment is quite often considered as a valid end-point to define treatment strategies, since finally OS is related to PFS in each of successive lines.

NSCLC PROGNOSTIC AND PREDICTIVE MARKERS

by David Rimm

The number of prognostic markers and predictive markers with clinical utility in lung cancer management has dramatically increased over the past 10 years. While stage and grade were historically nearly all that was required, new drugs and new methods of tissue analysis have changed the landscape. This presentation will first discuss companion diagnostic tests and their predictive value for specific therapies. These tests are largely DNA-based molecular tests and some data will be presented related issues in evaluation of testing methods. Then we will critically examine some new prognostic tests to evaluate their clinical utility.

THE EVOLVING TREATMENT LANDSCAPE OF NSCLC

by Alex A. Adjei

Non-small cell lung cancer (NSCLC) continues to be a major cause of cancer death worldwide. Systemic treatment has traditionally been cytotoxic chemotherapy, which had only modest efficacy. With the increasing knowledge in molecular biology and genomics, aberrant proteins that drive tumor growth have been identified, leading to striking efficacy when targeted drugs are used for these cancers. Genetic derangements that can be targeted include gene mutations (insertion, deletion, substitution and inversion) and chromosomal aberrations (deletion, inversion, duplication and translocation). A number of these aberrations affect protein targets against which there are active drugs. These so-called “actionable” mutations include BRAF, EGFR, EML4/ALK, HER2, RET, and ROS-1. Other potentially “actionable” aberrations against which efficacious drugs have not been completely validated include AKT, FGFR2, c-MET, MEK1 and PIK3CA. While promising,

these aberrations are finite and its likely that all actionable abnormalities (incidence greater than 1 %) have been discovered. There are unfortunately going to be a number of NSCLC tumors (could be as high as 40% of all tumors) for which there will not be actionable mutations detected. Agents affecting ubiquitous processes such as protein chaperones, apoptosis, hypoxia and tumor metabolism, in addition to immunologic targets will need to be incorporated into cancer therapy.

TRANSLATING LUNG CANCER BIOLOGY TO THE CLINIC

by Adi Gazdar

The onset of our rational understanding of the biology of lung cancer and its translation to the clinic started in 1970 and continues today at a greatly accelerated pace. Conventional texts of lung cancer biology usually describe a series of individual genes or pathways. An alternative way is to divide the period 1970 to the present as representing 5 decades of continuous progress, with a pivotal event commencing or greatly accelerated in each decade. As such, Fred Hirsch and myself have chosen the pivotal events outlined below. These five pivotal events offer a framework to describe the entire spectrum of lung cancer biology and its application to clinical care.

The 1970s – The Development of In Vivo and In Vitro Model Systems. Twenty years after George Gey established HeLa cells, the first lung cancer cell lines originated and large comprehensive panels were established in subsequent decades, along with immortalized respiratory epithelial cells, and widely distributed to the scientific community. Xenograft models at subcutaneous, orthotopic and other sites in immunocompromised mice were established and are widely used to test therapies. Genetically engineered mouse models have proved very useful for studying the pathogenesis, prevention and therapy of lung cancer.

The 1980s - The Decade of SCLC. Because of the availability of a large cell line panel, the initial focus was on SCLC. The observation of a specific cytogenetic abnormality, deletion of chromosome 3p, led to the identification of multiple tumor suppressor genes. *MYC* family amplification was identified as a frequent event in previously treated cases. The crucial roles of *TP53* and *RB* as early, initiating events were observed. The neuroendocrine properties and specific hormone products were described, as was the pivotal role of ASCL1 in controlling NE differentiation.

The 1990s – The Decade of NSCLC. As clinical progress in treating SCLC waned, the focus of attention switched to NSCLC. NSCLC demonstrates much more heterogeneity than SCLC, and progress was slower and less comprehensive, especially for squamous cell carcinomas, with its paucity of model systems. Similarities and differences of molecular changes between SCLC and NSCLC were noted. For instance cell cycle perturbations are common or universal to all lung cancers, but the mechanism differs between SCLC and NSCLC. *KRAS* mutations received much attention. Important findings regarding methylation, gene expression and allelic loss were observed, and later extended to SNPs and microRNAs. The importance of epithelial – stromal cell interactions, angiogenesis and epithelial-mesenchymal alterations were noted. The appearance of widespread molecular changes in histologically normal respiratory epithelium was observed. Lung cancer in never smokers had a different molecular pathogenesis than cancer in ever smokers.

The 2000s – The decade of Targeted Therapies. The identification of specific mutations in adenocarcinomas, especially *EGFR* and *ALK* translocations, has made lung cancer the poster child for the targeted therapy of solid tumors. Unfortunately, the dramatic initial clinical responses invariably are followed by the development of resistant tumors. However the major advances, resulting from the combination of molecular and biological studies, pharmaceutical developments and clinical applications, have stimulated an enormous body of work in all of these areas.

2010 to the Present – the decade of Comprehensive, Integrated "Panomics". The brief period since 2010 has been characterized by major advances in the biology of lung cancer due to the application of new whole genome technologies ("Panomics") in an integrated fashion. These advances have been driven by a) major improvements in technology, permitting genome wide studies utilizing multiple platforms, especially by ultra-deep sequencing of DNA and RNA; b) Application of the new technologies has led to the publication of large integrated multimodality studies of the three major forms of lung cancer; c) The availability of multiple large publically accessible databases regarding lung cancers and other samples has been a boon for lung cancer research. The convergence of these applications has generated huge amounts of data and led to major new

therapeutic applications. However, this vast, ever growing "mother lode" of biological information has only been superficially tapped with most of the data remaining to be mined and "translated" into clinical applications.
Despite this quantum leap in our knowledge, its full application to clinical care will require much further work and ingenuity. Some major outstanding applications include: a) identification of suitable therapeutic targets for SCLC; b) identification of actionable targets, preferably multiple, for all NSCLCs; c) the development and application of suitable methods for overcoming drug resistance; d) the ability to store, interpret and apply the huge amounts of data we are capable of generating about individual tumors. Thus, as we are entering the Golden Age of the Biology of Lung Cancer, major challenges remain. Overcoming these challenges will require close collaborations and large multimodality studies performed by interacting teams of researchers, clinicians, pharmaceutical companies and support by funding agencies.

EARLY CLINICAL DEVELOPMENT, A CRITICAL MOMENT FOR DRUG SUCCESS

by Jean-Pierre Armand

Advances in molecular oncology and cancer genetics in the last 20 years have defined many of the key driving oncogenes in human cancer, and most of common cancers are currently being revisited on the basis of modern molecular portraits that allow the identification of new molecular subtypes and new therapeutic opportunities. These hold the promise of greater clinical efficacy and fewer side effects when compared with traditional chemotherapeutic .Agents such as inhibitors of the BCR-ABL (imatinib), EGFR (gefitinib), BRAFV600E (vemurafenib) protein kinases or CYP17 inhibitors have transformed the treatment of chronic myelogenous leukaemia, non-small cell lung cancer, melanoma and prostate cancers respectively.
Many other molecular abnormalities have been reportedin genes such as TP53, RB1, CDKN2A, and STK11 tumor suppressor and in EGFR, KRAS and NRAS oncogenes , but also in PI3K, PTEN, AKT1, MDM2, APC, HER2, KDR, MET, CTNNB1, ATM, BRAF, AKT1 and more recently ALK, RET, ROS as well as FGFR1.

Molecular Medicine programs aim to provide targeted therapies taking into account the patient specific tumor genomic profile. Several clinical trials are ongoing to evaluate the concept of personalized medicine or molecular medicine. These trials will use genomic and proteomics approaches to discover molecular alterations predictive for sensitivity to moléculaire targeted therapies as well as developing an adequate molecular characterization of cancer for each patient. For example, MOSCATO (molecular-screening for cancer treatment optimization) is a prospective molecular triage trial designed to identify actionable targets and to match them with the selected targeted therapy. The final objective of this trial is to improve outcome.this IGR example is one example of the French cancer policy of INCA the French national cancer Institut.

In summary, characterization of the genomic changes that drive an individual patient's disease is now critical to inform rationally targeted therapies and treatment planning for patients with advanced cancer patients.

ADVANCES IN VACCINES IMMUNOTHERAPY

by Johan Vansteenkiste

Cancer immunotherapy in a broad sense is any interaction with the immune system to treat cancer.
A first approach is non-antigen-specific modulation of the immune system, historically with e.g. BCG, interferon, interleukins, etc., more recently with specific antibodies against Cytotoxic T-lymphocyte Antigen 4 (CTLA-4) or against Programmed Death 1 (PD-1) receptor or its ligands (PD-L1). Antigen-specific immunotherapy aims at specific priming of immune system to recognize the tu-

mour as foreign, thereby generating specific antibodies and/or cytotoxic T cells. This is "therapeutic cancer vaccination (TCV)".

Conditions for optimal TCV are: 1/ specificity (well-defined target antigen in the tumour, not in other tissues); 2/ selectivity (use in the population expressing the target); 3/ immunogenicity (interaction with antigen leads to effective humoral and/or cellular response); 4/ tumour sensitive to immune kill in order to obtain improvement in patients' outcome. Although the historical results of TCV for NSCLC were disappointing, knowledge from the last decades about the molecular pathology of tumours, of the immune system in general, and of tumour immunity in particular, has led to the introduction of several modern and more sophisticated TCVs. These vaccine formulations have shown encouraging data in phase II randomized clinical trials, and are now being studies in large phase III studies.
Important examples are the MAGE-A3 vaccine in resected early stage NSCLC, the BLP-25 vaccine in locally advanced NSCLC after chemoradiotherapy, and e.g. belagenpumatucel-L and the TG4010 vaccine in advanced stage NSCLC.

The MAGE-A3 protein is totally tumour-specific and present in about 35% of early stage NSCLC. In the hypothesis generating double-blind, randomized, placebo-controlled phase II study, 182 patients with completely resected MAGE-A3-positive stage IB-II NSCLC received recombinant MAGE-A3 protein combined with an immunostimulant (13 doses over 27 months) or placebo [1]. No significant toxicity was observed. There was a 24% - non-significant - improvement in disease-free survival (HR 0.76; 95% CI 0.48 to 1.21). Moreover, a predictive gene signature, initially described in advanced melanoma patients could be confirmed in early stage NSCLC [2].A large phase III study (n=2270) with MAGE-A3 vaccine is recruited and awaiting results (MAGRIT, NCT00480025).

Mucins like the MUC1 protein are present in many epithelia, but MUC1 expression is altered (mainly by aberrant glycosylation) in many cancer types, including NSCLC. The tandem repeat MUC1-peptide liposomal vaccine BLP-25 has been studied in patients with stage IIIB-IV NSCLC [3]. Patients in disease control after conventional treatment with chemo(-radio)therapy were randomly assigned to BLP25 (8 weekly s.c. immunizations, followed by administration at 6-week intervals) plus BSC or BSC alone. While overall survival (OS) was not significantly different in the total group, a challenging effect was observed in stage IIIB patients (HR 0.524; 95%CI 0.261-1.052). No significant toxicity was observed. At the 2013 ASCO meeting, the double-blind, randomized, placebo-controlled phase III study was presented (START, NCT00409188) [4]. Patients not progressing after primary chemoradiotherapy for unresectable stage III NSCLC were randomized to BLP25 or placebo. In the primary analysis population (n=1239), OS was better with the vaccine (HR 0.88, 95%CI 0.75-1.03). In the predefined subgroup analysis in patients after concurrent chemoradiotherapy (n=806) there was a median OS difference of 10.2 months (HR 0.78, 95%CI 0.64-0.95). While the most obvious role for TCV is for patients with small residual disease after treatment, several compound are in phase III testing in advanced NSCLC as well.

Belagenpumatucel-L is a vaccine based on a mixture of allogeneic tumour cells with TGF-β2 antisense blockade as adjuvant. In a phase II open trial, survival was related to the dose administered [5]. A phase III trial in patients with stage III-IV NSCLC in disease control after first-line therapy was reported at the 2013 ESMO meeting (STOP, NCT00676507) [6]. Patients without progression after 1st line chemotherapy, were randomly assigned to intradermal belagenpumatucel-L (N=270) versus placebo (N=262)for 24 months. Median OS was 20.3 months with belagenpumatucel-L versus 17.8 months with placebo (HR 0.94, p=0.594). In subgroup analysis of patients randomized <12 weeks after the last chemotherapy, the HR of the median OS was 0.77 (P=0.092). For patients enrolled within 12 weeks *and* treated with previous radiotherapy, the HR was HR 0.45 (P=0.014). The vaccine was well tolerated with mainly mild local administration side-effects.

TG4010 is a vaccine based on a recombinant viral vector (attenuated strain of vaccinia virus) expressing both the tumour-associated antigen MUC1 and interleukin-2. In a phase II randomized study, 148 patients with advanced NSCLC expressing MUC1 by immunohistochemistry received either up to 6 cycles of cisplatin-gemcitabine plus TG4010, or the same chemotherapy alone [7]. The primary endpoint, a 6-month progression-free survival more than 40% in the experimental arm was met. A confirmatory phase IIB-III trial is ongoing (TIME, NCT01383148).

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THE EXPANDING ROLE OF BEVACIZUMAB

by David Planchard

Tumour angiogenesis is critical for tumour progression. The vascular endothelial growth factor (VEGF) promotes angiogenesis and over expression of the VEGF has been correlated with poor prognosis in various malignancies, including NSCLC. Bevacizumab (Avastin®, Roche) is a recombinant, humanised, monoclonal antibody against the VEGF. Bevacizumab is an effective targeted therapy with demonstrated survival benefits for many patients with advanced nonsquamous non-small cell lung cancer (NSCLC). Evidence about its efficacy in addition to first-line chemotherapy in NSCLC has been produced by two large randomized phase III clinical trials (ECOG 4599 and AVAiL) and more recently in association with Pemetrexed (AVAPERL). Information from retrospective analysis and two large observational studies (SAIL and ARIES) have confirmed the safety profile of first-line bevacizumab with a wide range of chemotherapy partners, but whether its efficacy is comparable when combined with the different regimens is still unknown. Some patient populations are at higher risk for bleeding complications and bevacizumab should be avoided. Bevacizumab is generally a well-tolerated therapy that can be safely given in combination with multiple chemotherapy agents in the induction and maintenance phases of therapy. Adverse events associated with bevacizumab include hypertension, proteinuria, bleeding and neutropenia. The identification of predictive factors of efficacy would be relevant for the optimal use of the drug, but to date there are no predictive biomarkers of bevacizumab efficacy. Currently, the patient selection criteria are based on the risk factors associated with bevacizumab toxicity. Clinical research is still ongoing to define the role of bevacizumab in different settings, such as single-agent bevacizumab for continuation maintenance therapy in advanced disease, treatment beyond disease progression, adjuvant therapy in early-stage NSCLC or in combination with other targeted agents. We will discuss clinical trials of bevacizumab and developmental, and address the challenges of developing individualized treatment paradigms for NSCLC.

ANGIOGENESIS INHIBITION BEYOND BEVASIZUMAB

by Martin Reck

Tumour related angiogenesis, which is mediated by a variety of different pathways forms an obligatory prerequisite for tumour proliferation and metastasis. Therefore inhibition of neoangiogenesis represents an attractive target within the treatment of Lung Cancer as well as further solid tumours. Besides the monoclonal anti-VEGF antibody bevacizumab, which has shown efficacy in combina-

tion with chemotherapy in eligible patients with advanced non-squamous cell non small cell lung cancer (NSCLC) a number of additional antiangiogenic approaches have been investigated recently.
Ramucirumab, a humanized anti-VEGFR 2 antibody, with proven efficacy in pretreated gastric cancer is currently in investigation either in combination with platinum-based chemotherapy in first-line therapy or in combination with docetaxel in second-line treatment (REVEL trial). Both trials have completed the recruitment.
Furthermore a variety of antiangiogenic anti-VEGF tyrosine kinase inhibitors (TKIs) have been evaluated in different settings but most of the trials failed to reach their primary endpoint and none of the agents led to a significant improvement of overall survival (OS).
Recently the combination of the angiokinase inhibitor nintedanib with docetaxel showed a significant improvement of progression free survival (PFS) and OS in patients with adenocarcinoma compared to chemotherapy alone in a large randomized phase 3 trial of patients with pretreated NSCLC (LUME 1). Interestingly the best benefit was seen in poor prognostic patients fast progressing tumors and progressive disease as best response to first-line treatment.
Further trials are warranted to understand the translational background of these clinical results.

CETUXIMAB IN NSCLC: LESSONS FOR ALL

by Robert Pirker

Expression of the epidermal growth factor receptor (EGFR) is associated with poor prognosis in patients with advanced non-small-cell lung cancer (NSCLC). Thus EGFR blockade has been studied as a strategy to improve outcome in these patients.
Cetuximab was studied in combination with first-line chemotherapy in 2 phase III trials (1, 2). The FLEX study showed that the addition of cetuximab to first-line chemotherapy with cisplatin plus vinorelbine improved overall survival compared with chemotherapy alone in patients with advanced EGFR-positive NSCLC (1). The hazard ratio was 0.87 (p=0.04) and median survival times were 11.3 versus 10.1 months. The second phase III trial failed to demonstrate an improvement in progression-free survival for cetuximab added to chemotherapy with carboplatin plus a taxane compared to chemotherapy alone in unselected patients with advanced NSCLC (2). The benefit of adding cetuximab to first-line chemotherapy was then confirmed in a meta-analysis based on 2018 patients from 4 randomized trials in terms of overall survival, progression-free survival and response rates (3). The efficacy of cetuximab was independent of tumor histology and type of chemotherapy. Cetuximab-related side effects were skin rash and diarrhea but infusion reactions were rare.
Research then focused on the characterization of potential predictive biomarkers. Patients who developed early skin rash when treated with chemotherapy plus cetuximab were shown to have better survival than those who did not (4). KRAS mutation status, EGFR copy number and EGFR kinase domain mutations did not predict benefit from cetuximab (5). Consistent with other studies, however, EGFR-activating mutations were associated with good prognosis. EGFR expression based on an immunohistochemistry score was then shown to predict benefit from cetuximab (6). Among patients with high EGFR expression, patients treated with chemotherapy plus cetuximab had longer overall survival compared to those treated with chemotherapy alone: median 12.0 months versus 9.6 months; hazard ratio 0.73 (0.58–0.93); p=0.01. Among patients with low EGFR expression in their tumors, survival was not different between the two treatment arms. The treatment interaction test was significant (p= 0.04). The survival benefit in patients with high EGFR expression in their tumors was obtained without an increase in side effects. Recently, a subgroup analysis of the RTOG 0617 trial also suggested that patients with locally advanced NSCLC and a high EGFR immunohistochemistry score may benefit from the addition of cetuximab to chemoradiotherapy (7).
In conclusion, high EGFR expression level is a tumor biomarker that may predict survival benefit from the addition of cetuximab to first-line chemotherapy in patients with advanced NSCLC. A biomarker validation study is currently ongoing.

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CURRENT STATUS OF EGFR TKIs

by Filippo de Marinis and Antonio Passaro

In the last years, the treatment of Non-Small-Cell Lung Cancer (NSCLC) has deeply changed, due to utilize of Epidermal Growth Factor Receptor Tyrosine Kinase inhibitor. Indeed, with the understanding of lung cancer biology, and development of molecular targeted agents, there have been improvements in treatment outcomes for selected subsets of patients with non-small-cell lung cancer (NSCLC). In patients with advanced or metastatic non-small-cell lung cancer (NSCLC) carrying epidermal growth factor receptor (EGFR) positive mutations, the use of EGFR tyrosine kinase inhibitor (TKI) showed to improve survival and safety profile, when compare with standard chemotherapy. These results were reported in different randomized clinical trials with erlotinib as EURTAC and OPTIMAL, and with gefitinib IPASS, NEJ002, First-SIGNAL and the West Japan Thoracic Oncology Group Study. In these studies the median progression- free survival was around 10-12 months. After the results of the IPASS trial, gefitinib was approved for advanced NSCLC with EGFR positive mutation in all setting of treatment in Europa and Asia; while erlotinib that received in 2005 the indication in second- and third-line treatment in patients unselected for EGFR mutations after the Br.21 trial, recently was approved by FDA for the first-line treatment in patients with NSCLC harboring EGFR mutations, based on the results of the EURTAC trial in Europe, Asia and USA. In addiction to these interesting data, the results of LUX- Lung 3 and LUX-Lung 6 trial showed and confirm the activity of afatinib, an irreversible EGFR TKI, as front-line therapy in patients with EGFR positive mutations (mPFS of 13.6 months), compared with standard chemotherapy. All these results confirm that in patients with NSCLC harbouring EGFR mutations, EGFR TKIs, as afatinib, erlotinib or gefitinib, are the corner stone for the first-line treatment. In addiction to these results erlotinib, showed to be active in patients unselected for EGFR mutations, in second- and third line setting, after the results of the BR.21 trial, and in maintenance sitting, after a first-line chemotherapy in patients unselected for EGFR mutations. At the present time, second-generation of EGFR TKI are under evaluations in phase III trial, in patients harbouring EGFR mutations. Nowadays, it is mandatory to consider EGFR TKIs for the treatment of patients with EGFR mutations in first-line setting. In patients without EGFR mutations in second-line setting, erlotinib showed to be effective and should be consider as a valid therapeutic option to treat our patients.

MECHANISMS OF RESISTANCE TO EGFR TKI AND TREATMENT STRATEGIES

by Rolf Stahel

The treatment of advanced non-small cell lung cancer harboring activating EGFR mutations with EGFR tyrosine kinase inhibitors (TKIs) has led to a substantial improvement of survival. .It is recommended to treat patient with an activating EGFR mutation with an EGFR TKI in first line. There are three important issues to be considered in those patients. In the case of slowly progressing disease under EGFR TKI therapy one should consider continuation of the TKI beyond RECIST progression. In patients with localized progression radiotherapy and/or surgery should be part of the therapeutic approach. If the change to a conventional chemotherapy is mandated, this should consist of a platin-based combination therapy. Rebiopsy might be considered at this point to identify patients who might profit from one of the options detailed below. A large number of mech-

anisms of acquired resistance have been elucidated based on preclinical and clinical findings. One might divide these mechanism those which are potentially clinical relevant and on those which for the time being are of biological interest only. The predominant mechanism is the resistance mutation T790M which when very sensitive methods are employed can already be detected in up to half of the patients with activating EGFR mutation. Against expectations, second generation irreversible EGFR inhibitors alone have only marginal activity in overt T790M mutation positive tumors. However, afatinib, a second generation EGFR TKI, when combined with cetuximab has resulted in 30% objective responses in T790M positive tumors, but might be of limited use due to at times severe toxicity. Currently third generation mutation-specific EGFR inhibitors are under investigation and early results with CO-1686 and ACD-9291 look promising. Uncommon, but potentially targetable alterations associated with acquired resistance include MET amplification, HER2 amplification and BRAF mutation. A small proportion of tumors transforms to small cell lung cancer histology and thus might be best treated with platin-based combination therapy.

TARGETING HER2 AND BRAF

by Solange Peters

Research into the molecular basis of lung cancer has revealed insights into various critical pathways that are deregulated in lung tumorigenesis, and in particular the key driver genetic alterations that control cell survival and proliferation. The "oncogene addiction" model proposes that cancers harboring such gene amplifications, rearrangements or mutations rely upon the protein produced by the gene, which dictates their malignant phenotype, and can be thus referred to as a "driver alterations". Among them, BRAF and HER2 mutations are found in rare subsets of NSCLC. HER2 mutations consist of in-frame insertions in exon 20, leading to constitutive activation of the receptor and downstream AKT and MEK pathways. HER2 mutations were identified in about 2-4% of NSCLC. In the selected population of EGFR/KRAS/ALK negative patients, HER2 mutations can reach up to 6 %. This mutation is predominantly observed in females, non-smokers and adenocarcinoma subtype, similar to EGFR mutated NSCLC.

In our experience, upon retrospective review of 3800 patients tumour cancer genes anaylsis, we identified 65 NSCLC diagnosed with a HER2 in-frame insertion in exon 20. We collected clinicopathological characteristics, patient's outcomes and treatments. The HER2 mutation was identified in 65 patients (1.7%) and was almost an exclusive driver, except one single case with a concomitant KRAS mutation. All tumors were adenocarcinomas and 50% were stage IV at diagnosis. For these latter cases, 22 anti-HER2 treatments were administered after conventional chemotherapy in 16 patients. Subsequently, four progressive disease, seven disease stabilizations and eleven partial responses (overall response rate ORR 50%; disease control rate DCR 82%) were observed. Specifically, we observed a DCR of 93% for trastuzumab-based therapies (n = 15), 100 % DCR for afatinib (n = 3), but no response to other HER2-targeted drugs (n = 3).

BRAF mutations are reported in ~1–5% of NSCLC, almost exclusively adenocarcinoma. Mutations found in NSCLC are distinct from the melanoma setting: whereas BRAF-mutated melanoma harbors a V600E amino acid substitution in more than 80% of cases, NSCLC harbors non-V600E mutations in ~40%–50% of cases, distributed in exons 11 and 15. Remarkably, in recent reports, BRAF mutations were reported mainly in current or former smokers.

Screening 1046 patients with NSCLC, Marchetti et al. described BRAF mutations in 4.9% of adenocarcinomas and 0.3% of squamous NSCLC. In this series, patients with V600E BRAF mutations had a more aggressive tumor histotype- characterized by micropapillary features - and phenotype - with shorter disease-free survival and OS.

Current drugs targeting BRAF such as vemurafenib have been tailored to have specific activity against V600E mutant kinase, and their activity in NSCLC has been reported. In a single arm, phase II trial evaluating another BRAF inhibitor, dabrafenib, in 20 BRAF V600E NSCLC patients, 8 patients (40%) presented with a partial response, 4 patients (20%) with stable disease, 6 patients (30%) with progressive disease, and 2 patients (10%) were not evaluable resulting in an overall 40% response rate and 80% disease control rate.

These data reinforce the importance of HER2 and BRAF mutations screening in NSCLC and suggest that a specific targeted treatment should be proposed for this patient ideally within dedicated collaborative clinical trials.

EML4/ALK PATHWAY

by Ruth Palmer

Mammalian Anaplastic Lymphoma Kinase (ALK) was originally identified as a transforming oncogene associated with lymphoma. To date, many chromosomal rearrangements leading to an activated ALK have been described, and are implicated in a range of cancer types. The finding in 2007 that ALK is activated in lung cancer (NSCLC) has focused attention on ALK as a significant player in oncogenesis and bone fide target for drug development. Studies in lung cancer suggest that in the order of 35-60 000 NSCLC patients worldwide express an unregulated ALK protein. In addition to this high profile role in lung cancer, ALK is involved in numerous other tumour types, including both familial and sporadic neuroblastoma.
Given that inappropriate ALK signaling is now implicated in a wide range of tumour types, attention has focused on development of therapeutic strategies which may be clinically applicable. Most importantly, the development of tyrosine kinase inhibitors for use in cancer therapy has proven effective in several cases. Development of the first generation of ALK inhibitors has provided hope for a more targeted patient treatment, exemplified by the FDA approval of crizotinib (Xalkori) for use in ALK driven tumourigenesis. It is important to note that the next generation of ALK inhibitors appear to be effective against oncogenic ALK in which resistance mutations have developed within the ALK kinase domain. Our goal is to understand the molecular mechanisms underlying ALK pathology by combining mouse, human and Drosophila genetics. A concentrated focus on ALK should help us to better understand the significance of activated ALK for development of NSCLC as well as clinical strategies for the use of ALK inhibitors in this and other cancer types.

DETECTION AND MONITORING OF ALK-REARRANGED CTCS IN ALK POSITIVE PATIENT UNDER TREATMENT

by David Planchard

Emma Pailler, Julien Adam, Marianne Oulhen, Nathalie Auger, Alexander Valent, Melissa Taylor, Isabelle Borget, Fabrice André, Jean Charles Soria, Philippe Vielh, Benjamin Besse, Françoise Farace

The diagnostic test of ALK rearrangement in non-small-cell lung cancer (NSCLC) for crizotinib treatment is currently done on tumor biopsies or fine needle aspirations. The present study was designed to evaluate -1) whether ALK rearrangement diagnosis could be performed using circulating tumor cells (CTCs), -2) whether CTCs harbouring ALK rearrangement could be monitored in ALK-positive patients treated by crizotinib. CTCs were isolated in 18 ALK-positive and 14 ALK-negative patients by blood filtration and tested by Filter Adapted-Fluorescence In Situ Hybridization (FA-FISH), a FISH method optimized for filters. Numbers of ALK-rearranged cells and patterns of ALK-rearrangement were determined in CTCs and in tumor biopsies. ALK-rearranged CTCs and tumor specimens were characterized for epithelial (cytokeratin, E-cadherin) and mesenchymal (vimentin, N-cadherin) markers expression. ALK rearranged CTCs were monitored in ALK-positive patients treated by crizotinib. ALK-rearranged CTCs [ranging from 4 to 34 CTCs /1mL] were detected in all ALK-positive patients, while no or only one ALK-rearranged CTCs was detected in blood samples obtained from ALK-negative patients. ALK-rearranged CTCs harboured a unique (3' 5') split pattern while heterogeneous patterns (3' 5', only 3') of splits were present in tumors. ALK-rearranged CTCs exclusively expressed a mesenchymal phenotype and contrasted with heterogeneous epithelial and mesenchymal marker expressions in tumors. Variations in levels of ALK-rearranged CTCs and in CTCs harbouring a gain of *ALK* native copies were detected under crizotinib treatment. We demonstrated that *ALK*-rearrangement can be detected in CTCs of *ALK*-positive NSCLC patients, enabling diagnostic testing for crizotinib treatment. Our results suggest that CTCs harbouring a unique *ALK*-rearrangement and mesenchymal phenotype may arise from the clonal selection of tumor cells that have acquired the potential to drive metastatic progression of *ALK*-positive NSCLC. The molecular characterization of CTCs in patients undergoing crizotinib treatment might provide new insights into mechanism of resistance to ALK tyrosine kinase inhibitors, and possible strategies to overcome this resistance.

THE CLINICAL SIGNIFICANCE OF THE MET PATHWAY

by Enriqueta Felip

The molecular basis of lung cancer is complex and heterogeneous. Lung cancer develops through a multistep process involving multiple genetic and epigenetic alterations, particularly activation of growth promoting pathways and inhibition of tumor suppressor pathways.

The proto-oncogene MET located on chromosome 7q21-q31 encodes a membrane tyrosine kinase receptor, c-MET, that is also known as hepatocyte growth factor receptor. Upon the binding of c-MET receptor with its ligand, the hepatocyte growth factor, receptor homodimerization occurs, as does kinase activation and signaling through RAS/RAF/MEK/MAPK, PI3K/AKT and c-SRC kinase pathways. In NSCLC, MET amplification is observed in about 1-7% of patients and is more common in squamous cell carcinoma than in adenocarcinoma. The oncogenic activity of MET has been demonstrated in vitro with evidence of gene amplification associated with constitutive receptor activation of the PI3K/AKT pathway and sensitivity to MET inhibition. MET amplification is a known mechanism of acquired EGFR-TKI resistance in EGFR-mutated patients. In this scenario, MET amplification maintains the activation of PI3K/AKT pathway and bypasses the EGFR blockade by EGFR-TKIs, suggesting concomitant MET inhibition may be a way of overcoming EGFR-TKI resistance. Somatic mutations on the MET gene are uncommon and occur in approximately 1-2% of lung adenocarcinomas. Approximately 50% of NSCLC patients demonstrate high c-MET expression using immunohistochemistry and it has been associated with poor outcome.

At present, c-MET is considered an important target in anticancer therapy. Preclinical studies have shown that in animal models the inhibition of c-MET or neutralization of its ligand impairs the metastatic properties of cancer cells. Several molecules targeting c-MET, such as kinase inhibitors and monoclonal antibodies targeting either the ligand or the receptor, have been evaluated in early clinical trials. A relevant aspect in the development of c-MET inhibitors is the identification of molecular alterations predictive of the benefit of these drugs.

A number of c-MET inhibitors have entered clinical trials in NSCLC, among them tivantinib, cabozantinib, foretinib, crizotinib, rilotumumab, ficlatuzumab and onartuzumab. In a recently published phase II trial, previously-treated NSCLC patients were randomized to receive onartuzumab plus erlotinib or placebo plus erlotinib showing that MET-positive patients determined by immunohistochemistry achieved longer PFS and OS with the combination of erlotinib plus onartuzumab. The recruitment of a phase III trial in second/third-line of MET-positive patients by immunohistochemistry comparing erlotinib/placebo versus erlotinib/onartuzumab is now closed and the results are awaited.

As with other TKIs, c-MET inhibitors develop resistance. In this scenario, only preclinical data are available, and the resistance mechanisms described include the appearance of high-MET copy number, the amplification of wild-type MET and KRAS, and the acquisition of a point-mutation in the activation loop of c-MET.

In summary, several studies suggest that c-MET may well be a relevant target for personalized therapy in NSCLC and that identification of aberrant MET activity biomarkers could prove useful in the selection of patient subgroups that may benefit from c-MET inhibition. A future challenge is to define the molecular mechanisms of c-MET inhibitor resistance that will lead to further improvements in anticancer therapies, probably targeting more than one pathway.

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THE CLINICAL SIGNIFICANCE OF THE PI3KINASE PATHWAY IN NSCLC

by Alex A. Adjei

Phosphatidylinositide 3-kinases are a family of related intracellular signaling enzymes which phosphorylate the inositol ring of phosphatidylinositol (PtdIns). The PI3K family comprises three classes: Class I, Class II, and Class III. The classifications are based on primary structure, regulation, and in vitro lipid substrate specificity. Class I PI3Ks are heterodimeric molecules composed of a regulatory and a catalytic subunit, and the most studied in NSCLC. They are further divided into class IA and IB subsets based on sequence similarity. Class IA PI3K is composed of a heterodimer between a p110 catalytic subunit and a p85 regulatory subunit. There are five variants of the p85 regulatory subunit, and three variants of the p110 catalytic subunit, which are designated as a p110α, β, or δ catalytic subunit. These catalytic subunits are expressed by separate genes (PIK3CA, PIK3CB, and PIK3CD for p110α, p110β, and p110δ, respectively). PIK3CA is the most studied isoform, and estimates suggest that activating mutations in the p110α catalytic subunit occurs in up to 30% of all human cancer, with a reported frequency of up to 12% in squamous cell lung cancer. Unlike other activating mutations, PIK3CA mutations often exist with other oncogenic mutations such as KRAS, EGFR as well as tumor suppresor mutations such as PTEN. Based on these complexities, it is not surprising that efficacy of PI3 Kinase inhibitors have not been as robust or as directly correlated with activating mutations as seen with other activating mutations. The complexities of this pathway and early clinical results will be discussed.

SQUAMOUS CELL CARCINOMAS

by Rafal Dziadziuszko

Squamous-cell lung carcinoma represents approximately 20-50% of lung cancer cases depending on geographical location. Substantial efforts over last decade led to the identification and preclinical verification of several promising molecular targets for novel therapies.
The most important molecular abnormalities that undergo preclinical and clinical validation include FGFR1 amplification, FGFR2 and FGFR3 mutations, DDR2 mutation, EGFRvIII mutation, PIK3CA point mutation and amplification, and BRAF mutation. Other important non-kinase targets in squamous–cell carcinoma include SOX2 and NFE2L2 transcription factors.
Proper selection of patients into clinical trials evaluating inhibitors of particular pathway represents a challenge, especially with regard to definitions of clinically important high gene copy number/amplification. While the results of these studies are eagerly awaited, no targeted therapy is currently used in practice in patients with squamous-cell carcinoma of the lung.

SMALL CELL LUNG CANCER

by Andrea Ardizzoni

Small cell lung cancer (SCLC) accounts for 10-15% of all lung cancers with a steady decrease in incidence in the last two decades, probably due to smoking habit reduction. SCLC is highly sensitive to chemotherapy and radiation, representing a potentially curable tumor in a small fraction of patients with limited disease at presentation. Platinum/etoposide-based chemotherapy, combined with thoracic radiotherapy and prophylactic cranial irradiation in limited disease, remains the standard of care first-line treatment. However, despite high response rate with first-line treatments, the majority of SCLC patients relapses with an extremely poor survival outlook. In these patients, second-line chemotherapy improves quality of life and overall survival and topotecan still represents in EU the only approved agent in this setting.

However, since the introduction of platinum-based combination chemotherapy in the early '80s and of topotecan in late '90s no better drug therapy, either chemotherapeutic agents or molecular targeted agents, have been developed. Personalized treatment in first-line is achieved by considering mainly tumor-related factors, such as tumor extension and volume, and patient-related factors such as age, PS and comorbidities. In second-line, treatment outcome is highly influenced by factors related to first-line treatment outcome (treatment-free interval) and patient-related factors, such as presence of liver metastases, PS and blood levels of albumin and sodium. Using a prognostic score based on these parameters, it is possible to select patients who may benefit most from second-line topotecan and those who are better candidate for experimental treatment strategies.

NEUROENDOCRINE TUMORS OF THE LUNG

by Dan Granberg

Lung neuroendocrine tumors constitute a heterogenous group of malignant tumors with a varying clinical presentation and course of the disease. They are traditionally divided according to the WHO classification in terms of typical and atypical carcinoid, large cell neuroendocrine carcinoma and small cell lung carcinoma. The diagnostic criteria for typical carcinoid is carcinoid morphology with less than 2 mitoses/2 mm^2 (10 HPF) and no necroses. An atypical carcinoid is defined as a tumor with carcinoid morphology with 2–10 mitoses per 10 HPF and/or necroses. Large cell neuroendocrine carcinomas have more than 10 mitoses (median 70) per 10 HPF and cytologic features of a large cell carcinoma. Small cell neuroendocrine carcinomas have very high numbers of mitoses (median 80) per 10 HPF. Recently, the European Neuroendocrine Tumor Society has tried to apply a new classification system for lung carcinoids using similar cut off levels of the proliferation marker Ki67 (MIB-1) as for gastrointestinal neuroendocrine tumors.

This presentation will concentrate on typical and atypical lung carcinoids, the two more benign forms of neuroendocrine lung tumors. Radical surgery, including lymph node dissection, is the only curative treatment and is possible in most patients. The treatment for patients with metastatic lung carcinoids depends of the histopathology (typical/atypical), the extent of the disease, the proliferative rate (Ki67), the expression of somatostatin receptors and the performance status of the patient. There is no standard of care based on randomized controlled trials, yet several treatments have demonstrated activity in non-controlled studies. In previous days most of these patients were treated with chemotherapy such as Streptozotocin plus 5-FU or Doxorubicin. More recent data indicate that Temozolomide, either as monotherapy or combined with Capecitabine might be superior to the previous chemotherapy regimens. Another new type of treatment is the mTOR inhibitor Everolimus which has demonstrated activity in lung NETs. PRRT with ^{177}Lutetium-DOTATATE is also active in lung carcinoids and is an alternative for patients with strong somatostatin receptor expression and less than 20% Ki67-positive cells. Patients with slow growing tumors, proliferation less than 5%, might be treated with biotherapy including somatostatin analogs alone or combined with alpha-interferon. Patients with high proliferative tumors, >20%, should receive a combination of Temozolomide plus Capecitabine or platinum-based chemotherapy. Lung neuroendocrine tumors might present endocrine symtoms such as the carcinoid syndrome, Cushing's syndrome or acromegaly. Patients with the carcinoid syndrome or acromegaly are treated with somatostatin analogs in addition to the general antitumor therapy, and patients with Cushing's syndrome are usually subjected to bilateral adrenalectomy.

In conclusion, there are no randomized trials indicating the treatment of choice for patients with lung carcinoids. However, new therapies such as Everolimus as well as PRRT and Temozolomide-based chemotherapy are providing possibilities for a more personalized treatment for patients with metastatic typical and atypical lung carcinoids.

GENDER DISCREPANCIES OF LUNG CANCER

by Silvia Novello

At the beginning of 20th century only a few hundred cases of lung cancer were diagnosed annually, but the progressive huge spread of tobacco consumption caused a dramatic increase of the incidence of this disease among men and later on among female smokers. US data shows that the prevalence of smoking in American women peaked in 1965 at 33% and remained at that level throughout the 1970s, before beginning to slowly decrease in 1980. In contrast, more than half of American men smoked before 1965, but the prevalence dramatically decreased during the subsequent 20 years. Currently, 18% of American women smoke compared with 23% of men, reflecting the earlier and more marked decline in the prevalence of tobacco use in men.
Nowadays, more women in United States die from lung cancer each year than from breast, ovarian and uterine cancer combined: lung cancer is the leading cause of cancer death with more than 110,000 new cases and more than 72,000 estimated deaths in 2013.
In European countries, there are more than 79,000 new cases of lung cancer in female sex per year and 82,000 is the estimated death number in 2013, that means 9,024 more than what was reported in 2009.
Approximately 80% - 85% of lung cancers in women are caused by cigarette smoking. Wang et al. investigated the association of both active and passive smoking on lung cancer risk in a prospective cohort of more than 90,000 post-menopausal women: the results of the Women's Health Initiative Observational Study (WHI-OS) have been presented at 2013 ASCO annual meeting and evidenced an higher lung cancer incidence, particularly small cell lung cancers and squamous lung cancers, in current smokers (Hazard Ratio, HR 13.44, 95%, CI 10.80-16.75) and former smokers (HR 4.20, 95% CI 3.48-5.08) compared to never smokers. In the same study, among never smoking women, passive exposure, as an adult at home for $\geq$ 30 years, was associated with a trend of increased risk (HR 1.61, 95% CI 1.00-2.58) for lung cancer, confirming findings of previous prospective cohort studies.
Gender differences in terms of susceptibility to carcinogens and natural history of the disease have been reported and several case-control studies suggested that women are more vulnerable to tobacco carcinogens than men, even remaining this data controversial. Histological subtypes also differ significantly according to gender and in women adenocarcinoma is the commonest histologic subtype. When compared with men, women are more likely to be younger (50 years old) at the time of diagnosis and to have a better survival at any stage and independently from the therapeutic approach. Although tobacco smoking remains a significant risk factor for adenocarcinoma, approximately 20% of women with lung cancer are never smokers. Prevalence of lung cancer in females without history of tobacco smoking is estimated to represent 19% compared with 9% of male lung carcinoma in the United States. Estrogens may be involved in lung tumorigenesis through several mechanisms such as cell proliferation induced by ligand-estrogen receptor (ER) interaction, the cross-talk between estrogen receptors and other growth factor receptors (i.e. epidermal and insulin growth factor receptors). Hormonal status is one of the potential explanations for gender differences. Estrogens are involved in lung tumorigenesis and progesterone receptor expression has been described in non small cell lung cancers (NSCLC). Combinations of estrogen and progesterone work synergistically in vitro to promote vascular endothelial growth factor secretion increasing tumor-associated angiogenesis. Chlebowski et al. examined estrogen plus progestin (E+P) association with lung cancer incidence and outcome evaluating more than 30,000 postmenopausal women. Results have been presented at 2013 ASCO annual meeting: in non users of E+P, lung cancer incidence and deaths from lung cancer were significantly and substantially greater in current smokers versus never smokers ($p < 0.0001$ for both comparisons). In current smokers, lung cancer incidence and deaths from lung cancer were significantly and substantially greater in E+P users versus non-users ($p=0.0021$ and 0.0005, respectively), nearly doubling a smoker's already high risk of death from lung cancer.
The role of hormonal receptor in lung cancer needs more elucidations, but, based on preclinical data, some investigators already explored in phase II trials the implications of this pathway in the therapeutic scenario, adding for instance fulvestrant to an epidermal growth factor receptor tyrosine kinase inhibitor. There are several biomolecular differences in lung cancer, that are hypothesized to be responsible for gender differences such as a decreased DNA repair capacity in

women, a different expression of the X-linked gastrin-releasing peptide receptor (GRPR) and increased amounts of CYP1A1, having all these mechanisms a possible role in the increate risk for lung cancer development in women. An improvement in understanding genetic, metabolic, and hormonal factors that could affect the way women react to carcinogens and lung cancer represents a research priority.

With regard to specific gene alterations there are relevant differences in men and women. The most widely recognized is the epidermal growth factor receptor (EGFR) mutation, that is found at a much higher frequency in adenocarcinomas, women, Asians and never smokers. Mutations in HER2 gene, although much rarer, target the same subpopulations. Mutations in EGFR (and HER2) are mutually exclusive of K-ras mutations: these are primarily observed in smokers and historically associated with male sex, but there are also publications demonstrating an higher frequency in women of "non-classical" type of K-ras mutations even if these data need further validations. The echinoderm microtubule associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) translocation has been evidenced to occur more frequently in young patients, light or never smokers, while no major differences have been clearly stated between genders. B-Raf (V600) is described in 2% of patients with lung adenocarcinoma in western countries, related with worse prognosis and it is noted more frequently in women. An analysis of the p53 mutation databases indicated that the different spectra of p53 mutational patterns among smoker and never smoker cancers were almost entirely a result of differences between lung cancers in women, whereas male tumours did not show significant differences.

Finally, recent studies investigated the role of telomere shortening in lung cancer. Kim et al. hypothesized that relative telomere length may be associated with recurrence in early stage NSCLC after curative resection. Longer telomeres were significantly associated with higher risk of developing recurrence in female (HR 2.25; 95% CI, 1.02-4.96, P= 0.044) and adenocarcinoma subgroups (HR 2.19; 95% CI, 1.05-4.55).

All these findings provide multiple evidence for the specificities of lung cancer in women. The differential expression of specific biomarkers, which could be targeted by therapy, will improve research towards personalized sex-based investigations, stimulating the development of further gender-based approaches in thoracic oncology.

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Εκεί που η επιστήμη συναντά το πάθος, γεννιέται η καινοτομία.

Η συνεργασία με ανθρώπους εντός και εκτός της Novartis μάς δίνει τη δυνατότητα να διερευνήσουμε τόσο τη χρήση βιοδεικτών, όσο και την στοχευμένη ανάπτυξη σκευασμάτων για συγκεκριμένες ομάδες ασθενών.

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