General Information

Venue
The workshop takes place at the:

HILTON SORRENTO PALACE
Via Sant’Antonio 13
80067 Sorrento, Italy
T +39 081 8784141
www.sorrentopalacehotel.it

Language
The official language of the workshop is English.

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Congress Coordinator: Debora Urbinelli
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E-mail: d.urbinelli@meridiano.it
Aim of the live educational workshop

The Medical Education Initiative on Molecular Targeted Therapy of Cancer (MTTC), established in 2001 and directed by the International Education Council (IEC), was developed to provide high quality medical education programmes for medical oncologists, in response to the expanding knowledge of molecular biology and new targets for cancer therapy.

The Core Educational Curriculum comprises:

- Antibody-based therapy
- Signal transduction inhibition
- Angiogenesis inhibition
- Resistance to targeted therapies
- Cancer Immunotherapy

During this live educational workshop, internationally recognized oncology experts will present the latest developments in molecular biology, targets for cancer therapeutics and impact of new drugs in the clinic.

Learning objectives

After attending this live educational workshop, learners will be able to:

- Recognize the basics of signal transduction, angiogenesis and immunotherapy in cancer
- Summarize the latest developments in targeted therapies for cancer
- Describe the mechanisms at the basis of resistance to targeted therapy in cancer
- Illustrate the rationale of novel combination in molecularly targeted therapy for cancer
- Explain the current evidence in active and passive cancer immunotherapy

Target audience

Medical oncologists with an interest in the molecular basis of cancer, molecular targeted therapy and clinical application of the new drugs.

Accreditation

The “14th International Medical Education Workshop on Molecular Targeted Therapy of Cancer - Sorrento, Italy - 10-11 May 2013” has been accredited with 10 (ten) ESMO-MORA points Category 1.

SSIF SRL Società Scientifica di Formazione Internazionale Scientific Provider No. 13753 has submitted this programme “14th International Medical Education Workshop on Molecular Targeted Therapy of Cancer - Sorrento, Italy - 10-11 May 2013” for CME accreditation to the Italian National Commission for Continuing Medical Education in compliance with the procedures indicated by the Italian Ministry of Health.

Serono Symposia International Foundation (SSIF) adheres to the principles of the Good CME Practice Group (gCMEp)

All Serono Symposia International Foundation programmes are organized solely to promote the exchange and dissemination of scientific and medical information. No forms of promotional activities are permitted. All Serono Symposia International Foundation programmes are made possible thanks to educational grants received from: Arseus, Medical, Besins Healthcare, Bristol-Myers Squibb, Delgine, Centre d’E sclerosi M ultiple de Catalunya (Vall d’Hebron University Hospital), Centre Hépato-Biliaire, Hôpital Paul Brousse, ComteMed, Congrex, Croissance Conseil, Cryo-Save, Dataanalysis, Dos33, Esatoé, European Society of Endocrinology, Ferring, Fondazione Humanitas, Fundación IV, GE Healthcare, GlaxoSmithKline Pharmaceuticals, IPSEN, Johnson & Johnson, Medical, ISF International Society for Fertility Preservation, ISMH International Society of Men’s Health, K.I.T.E., Karl Storz, Lumenis, Merck Serono Group, PregLem, Richard Wolf Endoscopie, Sanofi-Aventis, Stallergenes, Stoptier, Teva Pharma, Toshiba Medical Systems, Université Catholique de Louvain (UCL), University of Catania.
We value your opinion!

We are continually trying to develop and improve our educational initiative to provide you with cutting-edge learning activities. During this live educational workshop you will be asked to answer a real time survey and after this educational workshop you will be receiving an online survey to help us to better tailor our future educational initiatives.

We thank you for participating!
Scientific Organizers

Heinz Zwierzina
Chairman of
the International Education Council (IEC)
Innsbruck Medical University
Innsbruck, Austria

Fortunato Ciardiello
Division of Medical Oncology
Department of Experimental and Clinical Medicine and Surgery F. Magrassi and A. Lanzara
Second University of Naples
Naples, Italy

International Education Council (IEC)

Jean Pierre Armant
Paris Cancer Institute
Paris, France

Wolfgang E. Berdel
Westfälische Wilhelms-Universität
Münster, Germany

Carsten Bokemeyer
University Medical Center Hamburg-Eppendorf
Hamburg, Germany

Markus Borner
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Bern, Switzerland

Fortunato Ciardiello
Division of Medical Oncology
Department of Experimental and Clinical Medicine and Surgery F. Magrassi and A. Lanzara
Second University of Naples
Naples, Italy

Anthony TC Chan
Department of Clinical Oncology
Prince of Wales Hospital
HK Cancer Institute and Sir YK Pao Centre for Cancer
Hong Kong, China

Leif Håkansson
Linköping University Hospital
Linköping, Sweden

Stan Kaye
Royal Marsden Hospital
Drug Development and Gynaecology Units
Sutton, Surrey, UK

Håkan Mellstedt
Cancer Centre Karolinska
Karolinska University Hospital
Stockholm, Sweden

Salvatore Siena
Dipartimento Oncologico
Ospedale Niguarda Ca’ Granda Milano
Milan, Italy

Jean-Charles Soria
Institut Gustave Roussy
Villejuif, France

Josep Tabernero
Vall d’Hebron University Hospital
Vall d’Hebron Institute of Oncology (VHIO)
Barcelona, Spain

Carlos Vallejos
Instituto Nacional de Enfermedades Neoplásicas
Lima, Peru

Eric Van Cutsem
University Hospital Gasthuisberg
Leuven, Belgium

Yosef Yarden
Weizmann Institute of Science
Department of Biological Regulation
Rehovot, Israel

Christoph C. Zielinski
Comprehensive Cancer Center, Vienna
General Hospital and Medical University of Vienna
Vienna, Austria

Central European Cooperative Oncology Group (CECOG)

Heinz Zwierzina
Chairman of
the International Education Council
Innsbruck Medical University
Innsbruck, Austria
## Scientific Programme

**Friday - 10 May 2013**

### Welcome and introduction

**Chairmen:** H. Zwierzina [Austria] - Y. Yarden [Israel]

### Session I  Inhibition of EGFR family pathways: activity and resistance

**Chairmen:** Y. Yarden [Israel] - S. Marsoni [Italy]

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
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<tbody>
<tr>
<td>10.40</td>
<td>L2</td>
<td>Targeting EGFR with Tyrosine Kinase Inhibitors and Monoclonal Antibodies</td>
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<tr>
<td></td>
<td></td>
<td>F. Ciardiello [Italy] - E. Van Cutsem [Belgium]</td>
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<tr>
<td>11.00</td>
<td>L3</td>
<td>Present and Emerging Treatment Options in Her-2/neu Overexpressing Metastatic Breast Cancer</td>
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<td></td>
<td></td>
<td>C. Zielinski [Austria]</td>
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<tr>
<td>11.20</td>
<td>L4</td>
<td>Resistance to EGFR and HER2 targeted therapies</td>
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<td>A. Bardelli [Italy]</td>
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</table>

### Hot topic discussion session

**Moderators:** Y. Yarden [Israel] - S. Marsoni [Italy]

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<thead>
<tr>
<th>Time</th>
<th>Discussion</th>
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<tbody>
<tr>
<td>11.40</td>
<td>How can we overcome EGFR targeted therapies resistance?</td>
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<tr>
<td></td>
<td>Panel discussion</td>
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<td></td>
<td>A. Bardelli [Italy]</td>
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<td>E. Van Cutsem [Belgium]</td>
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<td>C. Zielinski [Austria]</td>
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</table>

### Lunch break

12.10

### Session II  Inhibiting downstream effectors

**Chairmen:** S. Kaye [UK] - C. Vallejos [Peru]

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<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
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<tr>
<td>13.10</td>
<td>L5</td>
<td>Treatment of Non Small Cell Lung Cancer</td>
</tr>
<tr>
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<td></td>
<td>C. Zielinski [Austria]</td>
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<tr>
<td>13.30</td>
<td>L6</td>
<td>BRAF and MEK Inhibitors</td>
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<td></td>
<td></td>
<td>C. Robert [France]</td>
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<tr>
<td>13.50</td>
<td>L7</td>
<td>PI3K-Akt-mTOR Pathway Inhibitors</td>
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<td></td>
<td></td>
<td>J.P. Armand [France]</td>
</tr>
</tbody>
</table>

### Discussion

14.10

### Coffee Break

14.25

### Session III  Inhibition of Angiogenesis

**Chairmen:** E. Van Cutsem [Belgium] - L. Häkansson [Sweden]

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
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<tbody>
<tr>
<td>15.05</td>
<td>L10</td>
<td>Angiogenesis Inhibition and new strategies to target angiogenesis in cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W.E. Berdel [Germany]</td>
</tr>
<tr>
<td>15.35</td>
<td>L11</td>
<td>Antiangiogenesis in central nervous system malignancies</td>
</tr>
<tr>
<td></td>
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<td>W. Wick [Germany]</td>
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</table>

### Hot topic discussion session

**Moderators:** E. Van Cutsem [Belgium] - L. Häkansson [Sweden]

<table>
<thead>
<tr>
<th>Time</th>
<th>Discussion</th>
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<tbody>
<tr>
<td>16.25</td>
<td>How can we overcome antiangiogenic therapies resistance?</td>
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<tr>
<td></td>
<td>Panel discussion</td>
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<tr>
<td></td>
<td>W.E. Berdel [Germany] - W. Wick [Germany]</td>
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</tbody>
</table>

### Disease oriented session

**Chairmen:** E. Van Cutsem [Belgium] - L. Häkansson [Sweden]

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<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
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<tbody>
<tr>
<td>16.50</td>
<td>L12</td>
<td>Advances in targeted treatment of ovarian cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. Kaye [UK]</td>
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</tbody>
</table>

### Discussion

17.20

17.30  End of the first day
### Scientific Programme

**Saturday - 11 May 2013**

**Session IV  Current issues in immunotherapy**

**Chairmen:** H. Zwierzina (Austria) - W.E. Berdel (Germany)

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>09.00</td>
<td>L13: Immunoregulation in cancer</td>
</tr>
<tr>
<td></td>
<td>L. Håkansson (Sweden)</td>
</tr>
<tr>
<td>09.20</td>
<td>L14: Cancer immunotherapy: current standards and future promises</td>
</tr>
<tr>
<td></td>
<td>H. Mellstedt (Sweden)</td>
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<tr>
<td>09.40</td>
<td>L15: Cellular immunotherapy of cancer</td>
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<td></td>
<td>C. Rossig (Germany)</td>
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</table>

**Hot topic discussion session**

**Moderators:** H. Zwierzina (Austria) - W.E. Berdel (Germany)

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<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>10.00</td>
<td>Are there biomarkers for immunotherapy?</td>
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<tr>
<td></td>
<td>Panel discussion</td>
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<tr>
<td></td>
<td>L. Håkansson (Sweden)</td>
</tr>
<tr>
<td></td>
<td>H. Mellstedt (Sweden)</td>
</tr>
<tr>
<td></td>
<td>C. Rossig (Germany)</td>
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<tr>
<td>10.30</td>
<td>Coffee break</td>
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**Challenge the expert session (I)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>10.50</td>
<td>L16: Implementation of biomarkers in early clinical drug development</td>
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<tr>
<td></td>
<td>S. Marsoni (Italy)</td>
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</tbody>
</table>

**Session shooter**

E. Martinelli (Italy)

(ESMO Young Oncologist Committee)

**Discussion**

**Challenge the expert session (II)**

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<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>11.20</td>
<td>L17: Genomic heterogeneity of tumors: new challenges for therapy</td>
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<td></td>
<td>Y. Yarden (Israel)</td>
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</tbody>
</table>

**Session shooter**

L. De Mattos-Arruda (Spain)

(ESMO Young Oncologist Committee)

**Discussion**

**Disease oriented session**

**Chairmen:** To be confirmed

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>11.50</td>
<td>L18: New targets for the treatment of</td>
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<tr>
<td></td>
<td>- metastatic colorectal cancer</td>
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<tr>
<td></td>
<td>F. Ciardiello (Italy)</td>
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<tr>
<td></td>
<td>- metastatic gastric cancer</td>
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<td></td>
<td>E. Van Cutsem (Belgium)</td>
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<tr>
<td>12.30</td>
<td>L19: Therapy of renal cell cancer - choosing the right sequence</td>
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<td></td>
<td>C. Bokeremeyer (Germany)</td>
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<tr>
<td>12.50</td>
<td>Discussion</td>
</tr>
<tr>
<td>13.05</td>
<td>Concluding remarks</td>
</tr>
<tr>
<td></td>
<td>H. Zwierzina (Austria) - F. Ciardiello (Italy)</td>
</tr>
<tr>
<td>13.15</td>
<td>End of the meeting and closing lunch</td>
</tr>
</tbody>
</table>
Biographies

Jean Pierre Armand
Paris Cancer Institute
Paris, France

Jean-Pierre Armand MD, MSc, certified in Medical Oncology, is the General Director of the Institut Claudius Regaud in Toulouse [2007 – …]. Dr Armand is presently in charge of the construction of a new cancer center, in a European research hub created in the Toulouse cancer campus. He is an active member of the Medical Oncology Community. Previously Head of Early Clinical New Drugs Programs and Medical Director Research and development at the Institut Gustave-Roussy, Villejuif, Dr Armand is involved in Phase I-II and III studies for the treatment of solid tumors. Dr Armand is active in the European Organization of Research and Treatment of Cancer (EORTC), past chairman of the EORTC protocol review committee. At the EMEA French Agency [AFSSAPS] he is the representative of Oncology at the AMM Commission, in charge of approval anticancer agents. He was President of the European Society for Medical Oncology (ESMO), Medical Director of the Federation of European Cancer Societies [FECS], President of the French Cancer Society [SFC]. He is Member of International Boards of the American Association for Cancer Research (AACR), Member of scientific committee of the American Society of Clinical Oncology (ASCO) and AACR, Member of board clinical trials at Institut National du Cancer (INCa), chairman of the president nominating committee of ESMO. He has (co)authored over 300 medical and scientific publications and 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”.

Alberto Bardelli
Department of Oncology
University of Torino
Medical School
Torino, Italy

Prof. Bardelli and his group have identified molecular profiles underlying the response to targeted therapies in metastatic colorectal cancer patients. Recently, Prof. Bardelli and colleagues discovered that KRAS mutations impart secondary resistance to anti-EGFR therapies in colon cancer and that the mutations can be detected non-invasively in the blood of the patients months before progression is measured by radiographic approaches. A future focus of his lab is to find appropriately tailored drug combinations to overcome acquired resistance to targeted therapies.
Prof. Dr. Wolfgang Berdel was born in Hamburg and received his medical training at the Universities of Hamburg, Munich and Freiburg, where he obtained his MD in 1979. He currently holds the position as Professor of Medicine and Chairman of the Department for Medicine/Hematology and Oncology, Hemostaseology and Pneumology at the University of Münster, Germany. Dr. Berdel’s scientific interest has been in preclinical development and early clinical evaluation of cytotoxic drugs and biologically active peptides modifying tumor growth. He co-developed the ether lipids [alkyl-lysophospholipids and thioether-phospholipids] and conjugates, a new class of anticancer drugs with the cellular membranes as their main target, and he was the first investigator to introduce this new group of compounds into early clinical trials in oncology. His laboratory also was the first to demonstrate extrahematopoietic activity of hematopoietic cytokines such as IL-3, GM-CSF, and G-CSF on the clonal growth of solid tumor cells. Before moving to Münster in 1997, Dr. Berdel was speaker of the first „Sonderforschungsbereich” proposal on gene therapy in oncology to the Deutsche Forschungsgemeinschaft (SFB 506), which was funded. His current research interest is in the field of molecular leukemogenesis and vascular targeting of solid tumors. Clinically Dr. Berdel concentrates on diagnosis and treatment of leukemia, lymphoma and solid tumors such as lung cancer. This includes coordination of multicenter trials in these diseases. He is co-chairman of the Study Alliance Leukemia (SAL).

Carsten Bokemeyer is Head of the Department of Oncology and Hematology and Pneumology at the University Medical Center Hamburg-Eppendorf in Germany. He is also Director of the University Cancer Center (UCCH) of Hamburg University. He received his medical training from the Hannover University, Germany. After an academic exchange year at Memorial Sloan-Kettering Cancer Center in New York, USA, Dr. Bokemeyer worked at the Departments of Hematology and Oncology at Hannover University Medical School, and at Tuebingen University in Germany. Dr. Bokemeyer’s main research interests include genitourinary malignancies, particularly germ cell tumors, as well as gastrointestinal cancers [treatment options, supportive care and late toxicity, the development of new drugs and biological agents and the development of new combination treatment regimens]. His experimental research has focused on molecular prognostic markers and the mechanisms of drug resistance in solid tumor models.
Fortunato Ciardiello is Full Professor of Medical Oncology and Head of the Laboratory of Experimental Therapeutics at the Cattedra di Oncologia Medica, Dipartimento Medico-Chirurgico di Internistica Clinica e Sperimentale, Seconda Università di Napoli in Naples, Italy. Dr. Ciardiello received his MD degree, his specialty training in medical oncology and his PhD degree in molecular biology and pathology from the University of Naples, Italy. He obtained research training for almost 5 years at the National Cancer Institute, NIH, Bethesda, MD, USA. Dr. Ciardiello received the “G. Venosta” Award from the Italian Foundation for Cancer Research (FIRC) in November 2000 for research on novel therapeutic strategies in cancer. Dr. Ciardiello’s research interests involve the role of growth factors and their specific receptors in neoplastic transformation and the development of novel therapeutic strategies targeting growth factor receptor signaling, and he has published over 110 original research articles in these areas. In addition, Dr. Ciardiello is an active member of several international scientific societies, including AACR, ASCO and ESMO, and serves on the editorial boards of the journals Clinical Cancer Research, Oncology Reports, International Journal of Oncology, and Signal: The Journal of the EGFR-Targeted Cancer Therapy.

Leticia De Mattos-Arruda is a medical oncologist and translational/clinical investigator. She has been working in Vall d’Hebron Institute of Oncology/Vall d’Hebron University Hospital as a investigator since 2009 since obtaining her M.D. degree and Medical Oncology specialty training in Brazil. She has been conducting translational research projects and clinical trials at the Breast Cancer Center/Medical Oncology department and the Phase I units. Remarkably, she developed her interest in the study of blood circulating biomarker research and intratumor heterogeneity.
Leif Håkansson is currently Associate Professor at the University of Lund, Sweden, and Consultant in Oncology and Head of the Division of Clinical Tumor Immunology at the University Hospital in Linköping, Sweden. He received both his MD and PhD at the University of Lund, and has since held various positions at both the University of Lund and the University Hospital in Linköping. Dr. Håkansson’s research interests include immune parameters of importance for response, monitoring and optimization of immunotherapy and biochemotherapy in various types of cancer, e.g. renal cell carcinoma, malignant melanoma and colorectal cancer. He has published approximately 75 peer-reviewed articles, given approximately 40 congress presentations on these and other topics, and holds several patents on methods for prediction and monitoring of immunotherapy of cancer. In addition, Dr. Håkansson is a member of several scientific societies, including the Swedish Society of Oncology and the Swedish Society of Medicine, and is Vice Chairman of the Biotherapy Development Association (BDA).

Stan Kaye is head of the Division of Clinical Studies at the Royal Marsden Hospital/Institute of Cancer Research, London. Until recently he was Head of the Drug Development Unit at Royal Marsden Hospital one of the largest Phase I trials units in the world. He has long experience in leading on clinical trials in ovarian cancer and has most recently been involved in the development of PARP inhibitors. He qualified in medicine in 1972 in London, and trained in medicine and oncology in London and Australia. He joined the Royal Marsden Hospital in September 2000 after 20 years at Glasgow University as head of Medical Oncology. His interests, apart from new drug development, are in ovarian cancer and drug resistance. The author of over 400 peer reviewed papers, he sits on the editorial board of 12 cancer journals, and over the past 20 years has chaired national and international committees within EORTC, MRC and CRUK.
Biographies

Ronald Levy

Department of Medicine
Oncology Division
Stanford University
Stanford, CA, United States

Dr. Ronald Levy is a Professor of Medicine at Stanford University. He obtained his bachelor’s degree in biochemistry from Harvard University in 1963 and his medical degree from Stanford University in 1968. He is an elected member of the National Academy of Sciences and the Institute of Medicine. Dr. Levy’s research has focused for more than 20 years on monoclonal antibodies to B cells. He was the first to successfully treat human lymphoma with a monoclonal antibody, and went on to make important contributions to the development of rituximab, for the treatment of patients with resistant low-grade lymphomas. He is currently conducting clinical trials of a lymphoma vaccine. His research concentrates on the study of malignant lymphoma, using the tools of immunology and molecular biology to develop a better understanding of the initiation and progression of the malignant process. Dr. Levy is using lymphocyte receptors as targets for new therapies for lymphoma. Dr. Levy has published over 275 articles in the fields of oncology and immunology. Dr. Levy has received international acclaim for his work using the body’s own arsenal to fight cancer. In 1982 he shared the first Armand Hammer Award for Cancer Research, and was later awarded the Ciba-Geigy/Drew Award in Biomedical Research, the American Society of Clinical Oncology Karnofsky Award, the General Motors Charles Kettering Prize, the Key to the Cure Award by the Cure for Lymphoma Foundation, the Medal of Honor by the American Cancer Society, the Evelyn Hoffman Memorial Award by the Lymphoma Research Foundation of America, the 2004 Damashek Prize from the American Society of Hematology and in 2009 he won the King Faisal International Prize.

Silvia Marsoni

Clinical Trials Unit - FPO
Institute for Cancer Research
Candiolo, Italy

Italian and graduated in Medicine at the University of Milan. PHD in Pharmacology at the Mario Negri Institute, Milan. Spent several years at the NCI in Bethesda were she was in charge Chief of the Investigational Drug Branch. In the last 10 years she has directed an Academic Research Organization (Sendo Foundation) dedicated to the early clinical development of new anticancer agents which conducted early clinical trials with a translational component. Currently she is the Director of the Clinical Trials Unit at IRCC, Candiolo - Turin.
Erika Martinelli

Medical Oncology  
Second University of Naples  
Naples, Italy

Erika Martinelli is PhD, MD a medical consultant at the Medical Oncology, Dipartimento Medico-Chirurgico di Internistica, Clinica e Sperimentale of the Second University of Naples. Dr Martinelli was awarded her degree as specialist in Medical Oncology in 2004 and her PhD in 2008. From September 2003 to October 2005 she completed her research training at Vall D’Hebron University Hospital, Barcelona, Spain, as ESMO (European Society of Medical Oncology) fellow, where was she involved in a translational program for developing new targeted agents in solid tumor and colorectal cancer. Her research interest include the development of new targeted agents against growth factors in a preclinical and early clinical studies mainly in colorectal cancer. In particular defining the possible biological markers of intrinsic or acquired resistance to treatments. She is an active member of ESMO.

Håkan Mellstedt

Cancer Centre Karolinska  
Karolinska University Hospital  
Stockholm, Sweden

Håkan Mellstedt, MD, PhD, is a professor of oncologic biotherapy at the Karolinska Institute and the Cancer Centre Karolinska (CCK) at the Karolinska University Hospital in Stockholm, Sweden [1999-]. He is senior consultant in the Departments of Oncology and Hematology, and is board certified in internal medicine, oncology, and hematology. He was professor of experimental oncology at Uppsala University and head of the Department of Experimental Oncology, Department of Oncology, Uppsala University Hospital, Uppsala, Sweden [1996-1999] and Administrative Director of CancerCenter Karolinska 1999-2010. Professor Mellstedt’s main areas of research are tumor immunology and immunotherapy, with a focus on the development of cancer vaccines, antibody and cytokine treatment in gastrointestinal and chronic B cell malignancies. Further, he has implemented a programme developing targeted therapy using small molecules for the treatment of lymphoproliferative diseases. He has a great interest in the development of biosimilars. Professor Mellstedt was awarded the Alfaferone Prize [Italy] in 1989 and the Jan Waldenström Award [USA] in 2001. Professor Mellstedt was the president of ESMO from 2006 to 2007, and chair of the ESMO Foundation from 2008 to 2011. From 1993 to 2000, he was the chair of the Swedish Medical Society of Oncology. He was a member of the Scientific Committee of the Swedish Cancer Foundation [1987-2000]. He was the chair of the Scientific Committee evaluating medical research at Radiumhospital/Rikshospital in Oslo, Norway, and chair of the Committee for Clinical Medical Research of the Norwegian Research Council. Professor Mellstedt is the chair of the Swedish Childhood Cancer Foundation, Scientific Secretary of the Cancer Society in Stockholm and King Gustaf V Jubilee Fund and Scientific Advisor of the Lundbeck’s Foundation [Denmark]. He is member of the Accreditation Council of Oncology in Europe (ACOE) [2009-]. He is the co-founder of a biotech company, KANCERA AB, (2011) developing anti-cancer drugs. Professor Mellstedt has published about 500 manuscripts in peer-reviewed journals, is the author of numerous oncology chapters in professional medical textbooks, and has been an invited speaker at more than 190 international symposia. He is/has been on the editorial board of several international scientific journals. He holds several patents.
Peter Reichardt is Assistant Professor and Head of the Department of Interdisciplinary Oncology at the HELIOS Klinikum Berlin-Buch in Berlin, Germany, and is Director of the Sarcoma Centre Berlin-Brandenburg. He trained in internal medicine and haematology/oncology at the University of Heidelberg and at the M.D. Anderson Cancer Center, Houston, TX, USA. From 1992 to 2007, he was a Consultant at the Charité University Hospital in Berlin. Dr. Reichardt has led and conducted multiple clinical trials in gastrointestinal stromal tumour (GIST) in the adjuvant, advanced, and refractory settings. Dr. Reichardt is a co-author of the current European Society for Medical Oncology (ESMO) guidelines for the management of GIST, soft tissue and bone sarcomas and a member of the ESMO Sarcoma Faculty. Dr. Reichardt has contributed to numerous publications on soft tissue sarcoma and GIST management in leading oncology journals.

Caroline Robert is Head of the Dermatology Unit at the Institut Gustave-Roussy, Paris, France. Dr. Robert gained her medical degree at the Cochin Port-Royal School of Medicine, Paris, in 1990, after which she was made a faculty member of the graduate school of biological sciences and received her French Board Certification in Dermatology in 1992. On gaining her certification, Dr. Robert was appointed Assistant Professor in Dermatology at the St-Louis Hospital, Paris. She completed a research fellowship at Harvard, US and a PhD in cancer immunology and immunotherapy. In 2000, Dr. Robert returned to Europe as Medical Director for Johnson & Johnson Consumer Europe. In 2001, she took a position at the Institut Gustave-Roussy as Assistant in Dermatology, before becoming Head of the Dermatology Unit in 2005. She is board member for the European Association of Onco-Dermatology (EADO), melanoma board secretary for the European Organization for the Research and Treatment of Cancer (EORTC), a member of the European Association of Dermato-Venereology (EADV) and the French society of Dermatology and Venereology. Dr. Robert is a scientist of international renown in the clinical and translational research of melanoma and the cutaneous side-effects of new targeted chemotherapies. She has authored more than 120 articles in peer-reviewed scientific journals, including a number of publications on new treatments for metastatic melanoma and been involved in numerous international clinical trials.
Biographies

Claudia Rossig

Claudia Rossig received her medical degree at the University of Luebeck in Germany, then joined the Department of Pediatric Hematology and Oncology of University Children’s Hospital Muenster, Germany, as a Clinical Fellow. Between 1998 and 2000, she was a Postdoctoral Fellow with Malcolm Brenner in the Center for Cell and Gene Therapy, Baylor College of Medicine in Houston, USA. After finishing her clinical training as a Pediatrician in 2005 and her specialty registration as a Pediatric Hematologist and Oncologist in 2007, she is now attending physician and vice director of the Department of Pediatric Hematology and Oncology in Muenster. She is a member of the Pediatric NHL, ALL-BFM, and AML-BFM clinical study group steering committees. Her experimental research focuses on the development of cellular immune-therapeutic strategies to treat pediatric malignancies, including both leukemias and solid tumors.

Carlos Vallejos

Dr. Carlos Vallejos Sologuren is the General Director of the Instituto Nacional de Enfermedades Neoplásticas (INEN) and he was Health Minister of Perú, from July 2006 to December 2007. In 1996, he founded the Sociedad Peruana de Oncología Médica, being its first President until 1997. By the same time, he took the Presidency of the Chair of Oncocenter, and he was incorporated as Associate Academic of the “Academia Nacional de Medicina”. In 1998, he was reelected as President of the Sociedad Peruana de Oncología Médica, and the next year he took responsibility of the functions of consultant doctor of Medical Oncology in “Hospital Central de la Policía Nacional”; and he was regional delegate of the “Federación Latinoamericana de Sociedades de Cancerología”. In 1999, he created ONCOSALUD, the main private Enterprise that gives oncological services to Peru. One year later, he was chosen Principal investigator of Eastern Cooperative Oncology Group, one of the more important scientific organizations in the World, being at this time the only Latin-American Member with authorized voice. From December 2002 to July 2006, he got the role of General Head of INEN, starting a new approach to fight cancer and the decentralization process for oncological services in Peru. On July 2003, he was chosen as Regional Representative of the “Escuela Europea de Medicina Oncológica” (ESMO) for South America, and since that same year, he became part of the Editorial Committee of the Journal of Oncology. He is the author of the thesis “Mieloma Múltiple” (1968); and “Leucemia Aguda” (1987); besides the multiple scientific and academic articles published in several books and magazines related to oncology. Besides being researcher, he is coordinator of projects related to cancer treatment, working as speaker for multiple scientific and academic contests in this country and abroad. In Geneva, during his last session on 2008, he was chosen Vice-President of the Executive Committee of the Worldwide Organization of Health until 2009. In 2010, he has been named Director Member of the International Affair Committee of the American Society of Clinical Oncology – ASCO. In 2011 he has been named President of the Latin American and Caribbean Medical Oncology Society – SLACOM.
Biographies

Eric Van Cutsem

Eric Van Cutsem trained in internal medicine and gastroenterology in Leuven and specialised later in oncology in Leuven, Belgium. He is currently Professor of Internal Medicine at the University of Leuven and is head of the Digestive Oncology department at the University Hospital Gasthuisberg in Leuven, is board member of Leuven Cancer Institute and of the Department of Oncology at the University of Leuven. He has a large clinical activity in Leuven and is involved and leads many national and international clinical and translational research projects on gastrointestinal cancer. Prof. Van Cutsem has published more than 300 peer-reviewed articles (on PubMed; H-factor: 58) in prestigious journals. Eric Van Cutsem is a member of several scientific organizations, including ASCO, ESMO, European NeuroEndocrine Tumour Society (ENETS), European Society of Digestive Oncology (ESDO) and many national organizations. He is/was a member of the Scientific Program Committee and/or educational committee for ASCO, ASCO-GI cancers symposium, ESMO and ECCO. He is also a member of the ESMO faculty and joined the ESMO executive board on July 1, 2011. He is also chairman of the governmental colon cancer prevention task force in Flanders, Belgium and is president of BGDO (Belgian Group Digestive Oncology) and FAPA (Familial Adenomatous Polyposis Association). Eric Van Cutsem has been the founder of and is chair of the Scientific Committee of the World Congress on Gastrointestinal Cancer in Barcelona [in partnership with ESMO since 2005]. His major tasks and passions are at the moment taking care of patients with gastrointestinal cancer and trying to improve their outcome through organizing clinical and translational research projects.

Yosef Yarden

Born in Israel, Yosef Yarden received his B.Sc. in Biological and Geological Sciences from the Hebrew University of Jerusalem (1980), and a Ph.D. in Molecular Biology from the Weizmann Institute of Science (1985). His postdoctoral training was undertaken at Genentech, Inc. (c/o Axel Ullrich) in San Francisco, and at the Massachusetts Institute of Technology (c/o Robert A. Weinberg). In November 1988, he returned to the Weizmann Institute of Science as an Assistant Professor and was appointed Associate Professor in 1992, and Full Professor in 1996. Prof. Yarden currently serves as Chair of the Research Committee of the Israel Cancer Association. In January 2011 he was elected President of the Federations of Israel Societies of Experimental Biology (FISEB/ILANIT). In the past he chaired the Israel National Committee on Biotechnology, an advisory body of the Government of the State of Israel. Prof. Yosef Yarden focuses his research on the mechanism of action of growth factors, hormone-like molecules that play critical roles in embryogenesis, but also in tumor aggressiveness and invasion into surrounding tissues. His research is helping shed light on the way growth factors and their receptors promote tumor growth and metastasis, and is assisting attempts to combine therapies that target growth factor receptors with conventional therapeutic interventions.
Biographies

Wolfgang Wick

Department of Neuro-Oncology
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Wolfgang Wick, MD, is Chairman of the Department of Neurooncology and Director at the National Tumor Center at the University of Heidelberg, Germany. He is currently conducting multicenter phase III randomized trials for the Neurooncology Working Group (NOA) of the German Cancer Society and the European Organisation for Research and Treatment of Cancer (EORTC), as well as a number of multicenter trials with the pharmaceutical industry. He is a steering committee member of the NOA and the European Association for Neurooncology, as well as chairman of the EORTC Brain Tumor Group and member of the ECCO Board of Directors. His main scientific interests include migration and invasion of glioma cells, biomarkers, and radiosensitization. Professor Wick has written more than 180 publications in peer-reviewed journals, such as the Journal of Clinical Oncology, Lancet Oncology, Cancer Research, Nature, Nature Medicine, Neurology, Neuro-Oncology, Annals of Neurology, and Journal of Clinical Investigation.

Christoph C. Zielinski

Comprehensive Cancer Center, Vienna
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Christoph C. Zielinski completed his medical training at the University Hospital Vienna and began his career with a position as a research fellow at the Cancer Research Center at Tufts University, Boston, USA. He is Director of the Clinical Division of Oncology and Chairman of the Department of Medicine I at the Medical University Vienna, Austria. Since 2010, he also serves as Director of the Comprehensive Cancer Center of the Medical University and the General Hospital in Vienna, and is President of the Central European Cooperative Oncology Group (CECOG). He is a member of the American Society of Clinical Oncology (ASCO), the American Association for Cancer Research (AACR) and the European Society for Medical Oncology (ESMO) for which he acts on a series of committees as well as the local officer of the 2012 meeting in Vienna, Austria. His recent clinical research activities cover a wide range of cancer therapies, with particular focus on clinical trials, breast and lung cancer research and the treatment and development of targeted drugs. He is on the editorial board for a series of peer review journals which specialise in clinical or experimental oncology. He has published env. 450 original research papers and reviews in peer-reviewed journals.
Heinz Zwierzina

Chairman of the International Education Council (IEC)
Innsbruck Medical University
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Heinz Zwierzina is currently Professor at the Universität Innsbruck in Innsbruck, Austria. His main research interests are in the area of cancer therapy (cytokines, monoclonal antibodies, vaccines, inhibition of angiogenesis, and gene therapy), specifically of solid tumors, with a focus on colorectal carcinomas, breast cancer, lung cancer and sarcomas. Dr. Zwierzina has published over 80 original articles and book chapters on these and other subjects. In addition, Dr. Zwierzina was Board member of the European Organization for Research and Treatment of Cancer (EORTC), is the chairman of the Biotherapy Development Association (BDA) and is a member of the advisory board of the European Association for Cancer Research (EACR) and the Central European Cooperative Oncology Group (CECOG). Furthermore, he is a founding member of the International Committee for the Establishment and Development of Oncology Centers (ICEDOC), and is a member of numerous other international committees and scientific societies.
Abstracts
Growth factors and their transmembrane receptors contribute to all steps of tumor progression, from the initial phase of clonal expansion (cell proliferation), through recruitment of blood vessels to growing tumors (angiogenesis), and, eventually to migration and colonization of distant organs (metastasis). Hence, the information relay system involved in growth factor signaling provides potential sites for signal interception and tumor inhibition. A relevant example I will discuss comprises the epidermal growth factor (EGF) and the respective receptor tyrosine kinases, namely ErbB-1/EGFR and HER2, which belong to a prototype signaling module that drives carcinoma development. The extended module includes two autonomous receptors, EGFR/ErbB-1 and ErbB-4, and two non-autonomous receptors, namely: a ligand-less oncogenic receptor, HER2/ErbB-2, and a kinase-dead receptor [ErbB-3]. This signaling module is multiply involved in human cancer through autocrine loops involving co-expression of a receptor and one of the many EGF-like ligands, mutations and deletions within the EGFR gene, or amplification of either HER2 or EGFR.

In line with their extensive roles in tumor progression, growth factor receptors, such as EGFR and HER2 serve as targets for several cancer drugs. For example, the monoclonal antibodies Cetuximab and Trastuzumab recognize EGFR and HER2, respectively, whereas the kinase inhibitors Erlotinib and Lapatinib respectively block EGFR and HER2. My lecture will highlight examples of intracellular signaling pathways essential for survival and proliferation of tumor cells. In addition, I will focus on the inevitable evolution of resistance to cancer drugs, which often entails feedback regulatory loops.
L2 - Targeting EGFR with Tyrosine Kinase Inhibitors and Monoclonal Antibodies

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Abstract not in hand at the time of printing.
HER-2/neu+ breast cancer consists of a population of 10-15% of all women developing this disease. HER-2/neu positivity was a detrimental prognostic factor in the pre-trastuzumab era, but has turned into an important predictor for efficacy of HER-2/neu-targeted treatment which currently includes trastuzumab, lapatinib, in the very near future T-DM1 and – in combination with trastuzumab – pertuzumab. New formulations of trastuzumab allowing for a subcutaneous form of administration have been developed recently which will lead to a more patient-friendly form of application, as compared to the current i.v.-application without compromising treatment efficacy [HannA trial]. Other new and important steps include the addition of pertuzumab to trastuzumab which is intended to block heterodimerisation between HER-2 and HER-3 and have been shown to be superior in combination with docetaxel, as compared to a pertuzumab-free combination [CLEOPATRA trial]. This was true for not only progression-free but also for overall survival. Finally, the introduction of T-DM1 which consists of a trastuzumab part linked to the chemotherapeutic drug maytansine has shown to be significantly superior to a combination of capecitabine with lapatinib [EMILIA trial] in pre-treated patients as well as – in a randomized phase II trial – to trastuzumab + docetaxel in the first-line treatment of HER-2/neu overexpressing metastatic breast cancer.

The tyrosine kinase inhibitor lapatinib – although shown to be of significantly decreased efficacy in combination with a taxane, as compared to the combination of trastuzumab with a taxane regarding progression-free survival [MA.31-trial] – continues to have interesting indications in trastuzumab resistance, in the presence of CNS metastases from Her-2/neu overexpressing breast cancer and in specific endocrine situations when combined with an aromatase inhibitor.

Thus, new HER-2/neu-targeting drugs have dwelled upon previous impressive data on the efficacy of trastuzumab and expanded impressive results achieved with trastuzumab by the introduction of mainly pertuzumab and T-DM1 while simultaneously expanding previous observations on various possibilities of Her-2/neu – directed treatment options.
The advent of the EGFR-targeted monoclonal antibodies cetuximab and panitumumab has paved the way to the individualized treatment of metastatic colorectal cancer (mCRC). In the last 5 years it has become evident that mCRCs respond differently to EGFR-targeted agents and that the tumor-specific response has a genetic basis. After the initial response, secondary resistance invariably ensues, thereby limiting the clinical benefit of anti-EGFR therapies. Understanding the molecular bases of secondary resistance to cetuximab and panitumumab is required to design additional therapeutic options. We recently reported that molecular alterations (in most instances point mutations) of KRAS are causally associated with the onset of acquired resistance to anti-EGFR treatment in colorectal cancers. Resistant cells remain sensitive to combinatorial inhibition of EGFR and mitogen-activated protein-kinase kinase (MEK). Analysis of metastases from patients who developed resistance to cetuximab or panitumumab showed the emergence of secondary KRAS mutations in most of the cases. KRAS mutant alleles are detectable in the blood of patients as early as 10 months before radiographic documentation of disease progression. These results suggest the use of MEK inhibitors as a rational strategy for delaying or reversing resistance to anti EGFR therapies in mCRCs.
Non-small cell lung cancer (NSCLC) is responsible for more deaths than colorectal, breast and prostate cancer combined. The overall five year survival is a disappointing 10-15%. As chemotherapies have reached a plateau of efficiency, novel treatments and treatment options are highly desired. The latter have developed during the last few years by the introduction of targeted drugs on one and a change in chemotherapy strategies leading to the general acceptance of maintenance treatment on the other hand.

Targeted treatment including EGFR overexpression, EGFR mutation and MET/ALK mutation have led to the successful introduction of EGFR- and/or MET/ALK-targeting drugs in the clinic and have established NSCLC to consist of a multitude of a different subentities with divergent biologic behaviour. Currently available data suggest that treatment targeting molecularly decisive structures results in significantly better treatment responses than conventional chemotherapy used in the respective setting.

Considering the multitude of new molecular targets which have been identified and emerged in the analysis of NSCLC, the disease has to be considered a diagnostic and clinical challenge resulting in a careful choice of appropriate drugs for each biologic situation. This is true for already now, but even more so in the future when the results of an abundance of currently ongoing phase I, II and III trials will be available which examine the efficacy of a variety of targeted treatment options.

In addition to molecular targets and appropriate considerations, the efficacy of currently administered chemotherapy has been ameliorated by a change in treatment strategy represented by maintenance treatment which can consist of either cross-resistant or non-cross resistant chemotherapy or targeted treatment including erlotinib and gefitinib. Thus, maintenance treatment after the termination of the usual 4 to 6 courses of platinum-based regimens has been classified to represent a major step forward in the treatment of NSCLC by the majority of scientific societies.
Major advances have been made in the understanding of the biology of melanoma over the last decade. New predisposition genes have been identified and somatic key events such as the BRAF oncogene mutational status directly translate into therapeutic management. After decades of ineffective treatments, melanoma now appears as a “pilot” cancer for which two major and distinct strategies: immunotherapy and targeted therapy have recently demonstrated an impact on survival of patients with metastatic disease.

One of these strategies relies on the use of targeted therapies and is based on the fact that about 50% of melanomas harbor a recurrent activating BRAF V600E mutation. BRAF inhibitor vemurafenib is the first in line specific BRAF inhibitor and has demonstrated a positive impact on overall survival in patients with metastatic BRAF-mutated melanoma, rapidly followed by dabrafenib, which gives a similar improvement in PFS compared to chemotherapy. Both of these drugs induce frequent (more than 50% ORR), fast and important responses but PFS of the patients is around 6 months and most of them relapse in less than one year. Mechanisms of resistance are the subject of many recent high quality publications and one solution to avoid these resistance might be the concomittant use of BRAF and MEK inhibitors. Indeed, MEK blockade, downstream from BRAF on the same MAP-kinase pathway, with trametinib, is also effective in term of PFS and OS in this population of patients, but with a smaller objective response rate (22%). Combination of BRAF and MEK inhibition shows extremely promising response rates and duration of responses in early clinical trials. Phase III are presently enrolling patient, with, in the control arm, anti-BRAF monotherapy.

BRAF and MEK inhibitors have distinct safety profiles, and studies of their associated adverse events, like the paradoxical MAPK pathway activation by anti-BRAF agents is of major importance for our patients. Early developments combining these targeted agents with immunotherapies like ipilimumab or anti-PD1 are ongoing.

Thus the management of patients with metastatic melanoma is an extremely active and moving paradigm where the biology of the tumors as well as the underlying host parameters will have to be considered and where combination or sequencing of anti-BRAF and anti-MEK agents will have to be carefully evaluated.
Abstract not in hand at the time of printing.
L8 - Epigenetic Therapy and Synthetic Lethality with PARP Inhibitors

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A) Epigenetic Pathways

An alternative approach to molecular targeted therapy of cancer stems from the observation that the epigenetic inactivation [silencing] of key genes, whose function is crucial for normal cell growth, gives rise to malignant cells. Epigenetic inactivation [or transcriptional repression] is associated with chromatin alterations, caused by histone modification [deacetylation] and DNA methylation, and this can be reversed with various chemical agents, resulting in tumor growth inhibition and re-sensitization to chemotherapy. So far these agents have comprised demethylating agents [eg. azacytidine, decitabine] and histone deacetylase inhibitors [HDACs e.g. vorinostat, romidepsin]. Although these two classes have been approved for the treatment of certain diseases, i.e. myelodysplasia and cutaneous T cell lymphoma respectively, they have limited activity in solid tumors, and widespread applicability is unlikely because of lack of specificity. New targets for epigenetic therapy, including histone methyltransferase [e.g. EZH2] hold particular promise for more specific targeting; meanwhile the strategy of combining azacytidine with a HDAC inhibitor has shown intriguing clinical efficacy in patients with lung cancer, particularly in those with a molecular signature predictive of benefit [8].

B) DNA Repair Pathways

All cells, including cancer cells, need to continuously repair endogenous DNA damage and a number of repair pathways are involved in this. Experimental data have shown that cells which are deficient in one pathway, i.e. homologous recombination [HR], are susceptible to a novel form of anti-cancer therapy, described as tumour synthetic lethality, which involves inhibition of PARP [poly ADP ribose polymerase] [9]. These HR-deficient cells are characteristic of cancers arising from mutations of BRCA1/2.

Single agent clinical trials with the oral PARP inhibitor olaparib have demonstrated remarkable efficacy [approx. 50% clinical benefit] in BRCA-associated cancer patients [particularly ovarian and breast cancer] with an excellent tolerability profile [10-12]. There is likely to be a dose-response effect for these agents [for olaparib capsules, 400 mg bd appears to be the most effective dose]. HR deficiency may also be found in a larger group of patients than those with known BRCA-mutations, e.g. around 50% of cases of high grade serous [sporadic] ovarian cancer, and the search for robust biomarkers is intense. A randomized trial of the PARP inhibitor, olaparib, as a maintenance therapy in platinum-sensitive relapsed ovarian cancer has shown a positive benefit for this approach with preliminary data suggesting that the effect is most marked in those patients with germline BRCA 1/2 mutations [13]. Further trials in these patient are underway. Meanwhile, parallel studies are being pursued, involving PARP inhibitors in combination with chemotherapy. These require careful planning because of the potential for additional myelotoxicity, and no significant increase in efficacy was seen in the first randomized trial of the combination in patients with relapsed ovarian cancer [14]. On the other hand, treatment with single agent PARP inhibitors is set to make a significant impact on those patients with cancers identified as being HR deficient, especially those with BRCA mutations, and a number of agents in addition to Olaparib are now under active investigation.

References:
Soft tissue sarcomas consist of more than 50 different histological subtypes. All together, they are rare tumors with an incidence of 4-5/100,000, representing approximately 1% of all adult cancers with equal gender distribution. About 10% of the patients present with metastatic disease at the time of diagnosis, whereas 40 to 60% of patients with localised, high-grade soft tissue sarcoma will develop metastases, predominantly in the lungs, despite local control of the tumor. Median survival from the time of diagnosis of metastatic disease has been reported to be around 12 months.

Only few drugs have shown single-agent activity and gained approval in this indication including doxorubicin, epirubicin, ifosfamide, DTIC, trabectedin, and recently pazopanib. Combination chemotherapy has improved both response rate and progression-free survival in comparison to single agent therapy without impact on overall survival in first-line therapy.

Several new agents are currently studied in soft tissue sarcomas, including eribulin which has shown a nearly 50% progression-free rate at 12 weeks in adipocytic sarcomas. An ongoing phase III trial is comparing eribulin with DTIC in pretreated patients with liposarcoma or leiomyosarcoma. Ridaforolimus, an orally available mTOR inhibitor was evaluated as maintenance treatment in soft tissue and bone sarcomas resulting in a significantly prolonged progression-free survival compared to placebo. However, given the relatively small absolute benefit of appr. 6 weeks, the agent failed approval in this indication.

Whereas adult soft tissue sarcomas have been treated uniformly until recently, new strategies aim at developing specific treatment modalities for well defined subgroups of sarcomas. One of the first examples was the successful use of the specific tyrosine kinase inhibitor imatinib in gastrointestinal stromal tumors. Regorafenib was recently shown to significantly improve progression-free survival in patients with advanced gastrointestinal stromal tumors having failed imatinib and also sunitinib. Sorafenib was studied in soft tissue sarcomas in several trials. Activity was seen in angiosarcomas and leiomyosarcomas but not in other histological subtypes. Alveolar soft part sarcoma, an extremely rare subtype accounting for less than 1% of all soft tissue sarcomas is characterized by a t(X;17) translocation resulting in a ASPL-TFE3 fusion gene which encodes for an aberrant transcription factor leading to activation of MET. Based on these findings, both sunitinib, a multitarget tyrosine kinase inhibitor and tivantinib, a selective MET inhibitor have been studied with good results in patients with advanced ASPS. Inflammatory myofibroblastic tumors are mesenchymal neoplasms with an inflammatory infiltrate. Appr. 50% of these tumors carry rearrangements of ALK and have been shown to respond to the selective ALK inhibitor crizotinib, whereas tumors without ALK rearrangement did not respond. PEComa family tumors are characterised by mutations of TSC1 or TSC2 leading to activation of the mTOR pathway and treatment with mTOR inhibitors has resulted in responses in a number of patients.
The formation of new blood and lymphatic vessels is a critical determinant of tumor growth, spreading and metastasis. It plays a role in tumor support with nutrients, interaction between tumor cells and stromal elements, and removal of tumor waste products.

Tumors grow up to a size of 0.5 cm without neovascularization. Subsequently, they either recruit new endothelial cell precursors from the bone marrow for the formation of new vessels (vasculogenesis) or they induce formation of new vessels from preexisting vasculature (neo-angiogenesis). These processes are tightly regulated by a group of pro-angiogenic and anti-angiogenic molecules.

Neovascularization is supported by a plethora of factors, such as Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth Factor (bFGF), interleukin-8, and their respective receptor systems. Additionally, matrix metalloproteinases play a role in supporting the tissue invasion of endothelial cells. Antiangiogenic molecules such as angiostatin or endostatin are often present in the organism as fragments of larger proteins which may act as inactive storage forms. The inhibition of neovascularization by inhibition of neoangiogenesis or antivascular strategies is an attractive new approach to cancer therapy. Lymphangiogenesis inhibition is an area of active research in anticancer therapy.

Many new and promising therapeutic targets have been defined and studied. Preclinical trials including animal models have been very successful. Vascularization inhibition might be an ideal principle for combination with classical anticancer therapy modalities, such as chemotherapy or radiotherapy. Some compounds have shown meaningful response rates and prolongation of survival times in phase III trials; one monoclonal anti-VEGF antibody and several small molecules are approved for medical use by the drug authorities. Meanwhile, it seems to be important to better understand the molecular, cellular and pathophysiological events controlling neovascularization of tumors and the interaction of malignant cells with cellular and molecular elements of the tumor stroma. Development of resistance to antiangiogenic drugs in particular is a new and important field of molecular studies.
The vascular endothelial growth factor (VEGF) antibody bevacizumab (BEV) has increased the repertoire of medical treatment options for patients with recurrent glioblastoma. Two uncontrolled phase II studies [1,2] were the basis for approval in the USA in May 2009 whereas the European Medial Agency (EMA) rejected approval in the EU [3]. In the US the rate of objective responses (RR) [4] was accepted as a denominator for clinical relevance posing increasing weight on magnetic resonance imaging (MRI) as a surrogate marker for treatment efficacy. Anti-VEGF/VEGF receptor (VEGFR) compounds [5] at least as part of their mode of action induce normalization of the vasculature [6] by inhibiting pathological proliferation of endothelial cells and immature vessel formation. Secondly, as early as 1–2 days after initiation of therapy, a reduction of the permeability of the blood–brain-barrier results in decreased contrast enhancement and edema and high objective radiological response rates of 25–60% [1,2,5,7,8]. The makeup of the current as well as novel revised response criteria do not allow to easily differentiate this effect on the barrier permeability from a direct antitumor effect [9,10]. So far, the unprecedented high response rates these agents produced in recurrent glioblastoma have not translated into a survival benefit of the same magnitude [11]. Whether this is in part due to proinvasive effects of anti-VEGF compounds is a matter of debate [12].

In a current phase III – trial in newly-diagnosed glioblastoma, bevacizumab shows positive effects on progression-free survival with a maintained quality of life [13]. Data for overall survival are not mature yet, and will be presented at the ESMO conference in September 2013. Unexpectedly, other antiangiogenic compound classes, like tyrosine kinase-inhibitors are by far less effective and failed to show promising effects til date [14,15]. The often times strong anti-permeability effects of antiangiogenic drugs are particularly relevant for brain tumor therapy. First, they may reduce the brain edema by reconstituting the integrity of the blood–brain-barrier. Second, they generate difficult to interpret imaging results with the phenomenon of a pseudoregression in some patients, when there is a disconnect between a response in the T1-weighted contrast-enhanced MRI and the T2/FLAIR-weighted images. Future, so far unresolved questions concern the optimal combinations strategy with cytotoxic regimens, and the identification of a predictive biomarker.

References:
Ovarian cancer is the most lethal of the female gynaecological malignancies; however, modest improvements have been made and 5 year overall survival rate approaches 50% even though most cases present with disease spread beyond the ovary. Further improvements may be anticipated with the more widespread use of the anti-angiogenic agent Bevacizumab, following the reports of 3 positive randomised trials (incorporating maintenance treatment) in first line and relapsed disease. However, resistance to Bevacizumab will be a key problem and other approaches to anti-angiogenesis in ovarian cancer are actively being pursued.

A second area of significance is the introduction of PARP inhibitors, particularly for BRCA mutation-associated ovarian cancer. Taking advantage of the process of tumour selective synthetic lethality, these agents have demonstrated efficacy, particularly in maintenance therapy and registration trials are being planned.

Other targets in ovarian cancer include the alpha-folate receptor, which is over-expressed in most cases and the most promising approach to date involves an FR-targeted drug conjugate, Vintafolide. The PI3 Kinase/AKT pathway may also be a fruitful area, both as a single agent target in subgroups of ovarian cancer such as clear cell and endometrioid cancer, and in combinations aimed at reversing drug resistance. An anti-erbB approach, particularly targeting erbB3 is also under active exploration.

Some 10-20% of ovarian serous tumours are “low grade” and are characterised by mutations of the RAS/RAF/MEK family. This is leading to clinical trials with MEK inhibitors with initially promising results.

Overall ovarian cancer is increasingly being approached with targeted therapy; anti-angiogenics and PARP inhibitors are the most promising areas and other approaches in specific tumour types are actively being pursued.
The majority of human cancers can elicit immune-mediated anti-tumour reactivity and convincing data support a major role of the immune system in cancer control. Malignant tumours, however, can exploit a large number of immunoregulatory mechanisms to suppress immune mediated anti-tumour reactivity, such immunosuppressor mechanisms often appear at an early stage. Despite detailed knowledge of multiple such mechanisms it has not so far been possible to overcome cancer related immunosuppression resulting in efficient activation of the immune system against cancer. This presentation will deal with mechanisms whereby tumors manage to down-regulate immune-mediated anti-cancer reactivity.

The existence of regional immunosuppression in the absence of systemic suppression (concomitant immunity), indicates a regional - systemic gradient of immunosuppression. Accordingly, the function of immune cells is generally more impaired in the tumour than in peripheral blood. The impact of the hostile intra-tumoural milieu has been described by several groups. It is thus obvious that the immune reactivity against cancer can be suppressed at various levels, e.g. initiation, recruitment of effector cells to the tumour and migration of these cells within the tumour and their cytotoxic activity. The presence of effector mechanisms at the tumour site is an absolute requirement for immune mediated cancer control to occur.

The impact of the systemic immune status for cancer control can be demonstrated by determining pathological interleukin-6 production or infiltration of effector memory T-cells in the tumour, “The immune score”. Interestingly, the TNM-classification in colorectal cancer is not an independent prognostic marker when tested against “The immune score” in a multivariate analysis.

Currently, different types of immunosuppressor cells, regulatory T-cells, immature dendritic cells (iDC), tumour associated macrophages (TAM) and myeloid derived suppressor cells (MDSC), are discussed as the main players in cancer related immunosuppression. Suppression is mediated by the activity of enzymes such as IDO, arginase 1, NO-synthetase, their metabolites, oxidative stress/reactive oxygen species (ROS) and the expression of TGF-β, IL-10, CTLA-4 and PD-1/PD-L1. The immune balance is generally skewed to a Th2 dominance. However, over the years several other immunosuppressor mechanisms such as serum blocking factors, circulating immune complexes, enhanced IL-1Ra production and enhanced intratumoural proteolytic activity were identified to be of key importance. Any relevant model of immunosuppression must also incorporate these mechanisms.

Several therapeutic strategies have been applied but with limited success. Recently, however, modulation of CTLA-4 and PD-1/PD-L1 and vaccination against prostate cancer with sipuleucel-t has given promising results. Based on current knowledge, the efficacy of immunotherapeutic strategies can be significantly enhanced and considerable further improvement can be expected as immunosuppressor mechanisms in cancer are better understood.
Tumor cells express tumor antigens (TA) which might be regarded as “associated” i.e. part of the normal antigen repertoire but aberrantly expressed or as true TAs i.e. mutated or viral antigens. TAs might be utilized as targets for both passive (PSI) and active (ASI) specific immunotherapy. ASI augment the ability of the immune system to eliminate malignant cells. PSI includes monoclonal antibodies (MAb) and adoptive cell therapy. Aside from PSI, cytokines and a novel class of immunostimulatory MAbs that act directly on immune checkpoint control receptors (e.g. CTLA-4, PD-1) are also included.

Unconjugated antineoplastic MAb have three main effector functions: direct apoptosis, ADCC (antibody dependent cellular cytotoxicity) and complement lysis. The contribution of each of these effector functions for the total cell death for an individual MAb is not known. Eight anti-neoplastic MAbs have been approved both for the use alone or in combination with chemotherapy. Treatment with MAbs may be curative in diffuse large-B-cell lymphoma (DLBCL) and in adjuvant breast cancer.

ASI often referred to as “cancer vaccines” includes both prophylactic and therapeutic vaccines.

Prophylactic hepatitis B vaccination has reduced the incidence of hepatocellular carcinoma. HPV vaccination reduced the prevalence of HPV antigen positive individuals in the risk population which should reduce the incidence of cervical carcinoma by time.

Therapeutic cancer vaccines (TCV) or antigen specific cancer immunotherapeutics (ASCI) incorporate multiple components (e.g. TA, delivery system, adjuvants) to induce a robust Th1-type immune response. The complex function of the immune system has hampered the clinical progress of TCV/ASCI although remarkable activity has been seen in mice models. During the last years, progress has been made. The first approved TCV was sipuleucel-T (2010) for the treatment of asymptomatic/minimally symptomatic metastatic castration resistant prostate cancer. A number of phase II/III trials have however not met the primary end-point of the studies, in most cases overall survival for the total study cohort, but have shown in ad hoc analyses statistically significant benefits in subgroups indicating the need to identify patients responding to TCV/ASCI. Promising results have been seen in advanced melanoma, NSCLC, NHL, RCC, pancreatic cancer and glioblastoma.

To improve the clinical efficacy of ASI, TCV/ASCI should be administered in a more optimal way. TCV/ASCI should be combined with chemotherapy which might augment an immune response. Immunomodulatory agents should be added. Optimal patient populations should be selected and immune response evaluation criteria for immunotherapy should be applied.

Promising results have been reported using immunostimulatory MAbs. MAb against CTLA-4 on Treg (iplimumab) increased OS in advanced melanoma with 2 months and at 2 years there was a plateau at 20-25%. The MAb is also effective in NSCLC and SCLC. MAb against PD-1 on Treg (nivolumab) produced durable responses in patients (10-30%) with advanced RCC, melanoma and NSCLC.

With optimally designed immunotherapy trials there is a great likelihood that clinical results of immunotherapy will improve for the introduction in the clinic.
Cellular immunotherapy exploits the capacity of the immune system to effectively eliminate target cells while establishing an antigen-specific immune memory. One of the most convincing examples of cellular immunotherapy is the transfusion of donor lymphocytes in patients with myeloid malignancies which can effectively prevent disease relapse post allogeneic transplant. The development of immune-based strategies for cancer beyond the allogeneic context is challenged by the scarcity of T cells with high receptor avidity for tumor-specific antigens within the patient’s lymphocyte repertoire, and the failure of tumor cells to present antigen to T cells. Both obstacles can be bypassed by genetic modification of T cells with recombinant chimeric receptors (CARs) which redirect T cells towards a tumor surface antigen independent of antigen presentation. CAR reengineered T cells efficiently interact with tumor cells in vitro and have significant in vivo activity against tumor xenografts. Recently, first clinical trials have shown evidence for a potent antitumor activity of CD19-specific CAR T cells in leukemia. Current efforts focus on improving in vivo survival, functional persistence and potency of adoptively transferred anti-tumor T cells. The design of more effective strategies against both solid tumors and leukemias further depends on enhanced knowledge of specific mechanisms of immune escape. Moreover, rational combinations of targeted therapies with immunotherapies and optimal integration of cellular therapies into current treatment regimens may allow higher rates of durable responses.
Abstract not in hand at the time of printing.
Patient resistance to chemotherapy and molecularly targeted drugs is the major reason why most advanced solid tumors remain incurable. The recently achieved higher resolution and more rapid analysis of individual cancer genomes have shown bewildering intratumor heterogeneity (ITH), which may contribute to drug resistance. Accordingly, sequential analysis of tumors has proposed that ITH dynamically evolves during the disease course. Hence, tumor subclones that may ultimately influence therapeutic outcome may evade detection because of their absence, or because of their presence at low frequency at diagnosis. Evidence that cancer therapeutics may augment ITH, along with the need to track the tumor subclonal architecture through treatment, represent key questions. In conclusion, envisaging tumor growth as a Darwinian tree with the trunk representing ubiquitous mutations and the branches representing heterogeneous mutations may help in drug discovery. Likewise, identification of drivers or suppressors of ITH may provide attractive therapeutic targets to limit tumor adaptation.

Suggested literature:
New targets for the treatment of metastatic colorectal cancer  
Fortunato Ciardiello

Abstract not in hand at the time of printing.

New targets for the treatment of metastatic gastric cancer  
Eric Van Cutsem

Patients with gastric adenocarcinoma present frequently with large, unresectable or metastatic tumours at the time of diagnosis. For these patients, treatment is palliative and, in most cases, options are limited to systemic chemotherapy. The median survival with conventional cytotoxic chemotherapy does usually not exceed 8-12 months. Usually a doublet or triplet of cytotoxics is administered to these patients. The benefit of a second line chemotherapy has also been demonstrated recently with an impact, although modest, on survival. In the treatment of gastric cancer the fluoropyrimidines, platinum, taxanes, irinotecan and/or epirubicin are used in different combinations and sequence.

There is therefore a clear need for better treatment options. The search for targeted agents has been intensified recently. The doublet of 5-FU/capecitabine and cisplatin serves often as a backbone for the combination with novel targeted agents in the first line treatment. A significantly longer survival has been shown for the combination of a fluoropyrimidine/cisplatin plus trastuzumab in patients with a HER-2 positive gastric or gastro-oesophageal junction adenocarcinoma compared to the cytotoxic doublet alone. Trastuzumab has become the first active targeted agent with a proven activity in gastric cancer and the combination of trastuzumab plus a fluoropyrimidine and cisplatin has become the standard treatment in HER-2 positive metastatic gastric cancer. The ToGA trial was performed in patients with a HER-2 immunohistochemistry (IHC) 3+ or FISH positive tumor and showed indeed a significant survival benefit (13.8 versus 11.1 months; HR: 0.74). In patients with a strong HER-2 positive tumor (IHC 2+ and FISH positive or IHC 3+) an even larger survival benefit was shown (median survival: 16.0 versus 11.8 months; HR: 0.65). Angiogenesis inhibitors have studied recently. Bevacizumab has been studied in combination with capecitabine/cisplatin in a large phase 3 trial (Avagast trial). The trial showed a non-significant improvement in survival, but a significant benefit in progression free survival and response rate. Relevant geographic differences were shown with no benefit in Asian patients. An important biomarker programme is being done in this trial. Early data have suggested a potential predictive role for neuropilin and serum VEGF-A concentration. Ramucirumab, an antibody against the VEGFR2 receptor, has shown to improve the survival in second line treatment of metastatic gastric cancer. The epidermal growth factor inhibitors (EGFR) inhibitors cetuximab and panitumumab have failed to demonstrate a survival benefit when combined with chemotherapy in the first line treatment of gastric adenocarcinoma. The trial evaluating the activity of the mTOR inhibitor everolimus has failed to show a survival benefit in second/third line, although the progression free survival was prolonged. Several other targeted agents are under investigation in combination with cytotoxics: other angiogenesis inhibitors, the EGFR/HER2 blocker lapatinib and the new anti-HER2 antibody pertuzumab. Amongst other promising targets for new drugs in early development are the HGF (hepatocyte growth factor)/c-Met receptor and the FGFR (fibroblast growth factor) receptor.

These data show the promise for evaluating new targets in gastric cancer and show the need to unravel the relevant molecular targets and pathways and underscore the need of collecting tumour biopsies and blood samples of patients with gastric cancer.

References:
Several new agents have become available for the treatment of metastatic clear cell renal cell cancer. Established 1st-line options are interferon / bevacizumab, sunitinib, pazopanib as well as temsirolimus especially for high-risk patients. These current treatment approaches achieve progression free survival as 1st-line treatment in good prognostic patients of 7 to 8 months. A randomised study comparing pazopanib and sunitinib as 1st-line therapy has established similar efficacy but patient preference data in favour of pazopanib. Another new agent in 1st-line therapy is tivozanib. As acquired resistance to VEGFR blockage may occur during 1st-line treatment, subsequent treatment options for 2nd-line may be axitinib or the use of the mTOR inhibitor everolimus. Both have demonstrated activity in this setting, the best sequence is unknown. Trials such as SWITCH or RECORD-3 are trying to clarify the optimal treatment sequence. However, currently no best sequence of targeted agents can be determined based on evidence from randomised trials. However, it appears that using all available agents in a sequential way is useful to improve the overall prognosis of patients with metastatic renal cell cancer.
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