10th Latin American Medical Education Workshop on Molecular Targeted Therapy of Cancer

22 November 2013 - Sao Paulo, Brazil
General Information

Venue
The live educational workshop takes place at the:

PESTANA SAO PAULO HOTEL
www.pestana.com

Language
The official language of the live educational workshop is English.
Simultaneous translation is provided:
- From English to Spanish and vice versa
- From English to Portuguese and vice versa

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Aim of the live educational workshop

The International Education Initiative on Molecular Targeted Therapy of Cancer (MTTC) was initiated in 2001 with the aim of developing content for high quality medical education for oncologists. Based on the presentations of the first International Workshop on MTTC in Paris in 2002, an educational core curriculum has been developed, directed by the members of the International Education Council. This 10th Latin American Workshop on MTTC is an activity within the International Medical Educational Initiative on MTTC in Latin America, which began with the 1st Latin American Workshop on MTTC in Bariloche, Argentina (2003) and was followed by further workshops in Cancun, Mexico (2004), Trancoso, Brazil (2005), Pucón, Chile (2006), Rio de Janeiro, Brazil (2007), Buenos Aires, Argentina (2008), Quito, Ecuador (2009), Lima, Peru (2010) and Santiago, Chile (2011). A distinguished group of Latin American oncology experts from different disciplines will be giving educational presentations on the basic mode of action and clinical application of various targeted therapies.

Learning objectives

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

• Define the basics of signal transduction, angiogenesis and antibody-based therapy in cancer
• Describe the clinical applications of targeted therapy in cancer
• Summarize the latest developments in the fields of signal transduction, angiogenesis, and antibody-based therapy in cancer therapy

Target audience

Oncologists, radiation-oncologists, surgeons, pathologists.

We value your opinion!

We are continually trying to develop and improve our educational initiative to provide you with cutting-edge learning activities. 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!
Accreditation

Serono Symposia International Foundation (www.seronosymposia.org) is accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) to provide the following CME activity for medical specialists. The EACCME® is an institution of the European Union of Medical Specialists (UEMS), www.uems.net

The “10th Latin American Medical Education Workshop on Molecular Targeted Therapy of Cancer” held on 22 November 2013 in Sao Paulo, Brazil, is designated for up to 9 (nine) hours of European external CME credits. Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity.

Through an agreement between the European Union of Medical Specialists and the American Medical Association, physicians may convert EACCME® credits to an equivalent number of AMA PRA Category 1 Credits™. Information on the process to convert EACCME® credit to AMA credit can be found at: www.ama-assn.org/go/internationalcme.

Live educational activities, occurring outside of Canada, recognized by the UEMS-EACCME® for ECMEC credits are deemed to be Accredited Group Learning Activities (Section 1) as defined by the Maintenance of Certification Program of The Royal College of Physicians and Surgeons of Canada.

The “10th Latin American Medical Education Workshop on Molecular Targeted Therapy of Cancer” held on 22 November 2013 in Sao Paulo, Brazil, has been accredited with: 8, cat. 1 ESMO-MORA points.

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Scientific Organiser

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Carlos Vallejos
Chairman of the
Latin American
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Lima, Peru
## Session I: Introduction

**Chairs:** C. Vallejos (Peru) - C. Mathias (Brazil)

- **9.30** Welcome and Introduction to the Medical Education Initiative on Molecular Targeted Therapy of Cancer
  C. Vallejos (Peru)

- **9.50** L1: Clinical implications of molecular targeted therapies of cancer: where are we today?
  C. Serodio Baldotto (Brazil)

## Session II: Biological targets in the treatment of cancer

**Chairs:** J.M. Reyes (Chile) - P.M. Hoff (Brazil)

- **10.10** L2: Targeting the neoplastic cell, focus on cell receptors and signal transductions
  R. de Almeida Coudry (Brazil)
  B. Garicochea (Brazil)

- **10.30** L3: Targets of the cell environment: role of angiogenesis inhibition and resistance in cancer
  H. Gomez (Peru)

## Session III: Targeting the immune system

**Chairs:** G. Cinat (Argentina) - H. Gomez (Peru)

- **10.50** L4: Immunoregulation in cancer
  C. Silva (Argentina)

- **11.10** L5: Antigen specific immunotherapy in cancer
  H. Zwierzina (Austria)

- **11.30** Coffee break

## Session IV: The changing approach in treating cancer

**Chairs:** H. Luperia (Ecuador) - C. Canela (Venezuela)

- **11.50** L6: Advances in molecular diagnosis
  R. de Almeida Coudry (Brazil)

- **12.10** L7: Biomarkers in solid tumors
  J.M. Reyes (Chile)

- **12.30** L8: Biomarkers in hematologic malignancies
  J. León Chong (Peru)

- **12.50** Lunch

- **13.50** L9: New concepts in old targets: focusing on mechanism of resistance
  C.L. Arteaga (USA)

- **14.10** L10: New Drugs—New Side Effects
  J. León Chong (Peru)

- **14.30** Coffee break
Scientific programme

Session V  Clinical applications: from the lab to the clinic

**Chairs:** E. Mickiewicz (Argentina) - J. León Chong (Peru)

**14.40 - 16.40 Round tables - Part I**

**Table 1:** Molecular Treatment of NET  
J.M. Reyes (Chile)

**Table 2:** Molecular Treatment of Head & Neck Cancer  
C. Canela (Venezuela)

**Table 3:** Molecular Treatment of Breast Cancer  
H. Gomez (Peru)

**Table 4:** Molecular Treatment of Melanoma  
G. Cinat (Argentina)

16.40  Coffee break

**16.55 - 18.10 Round tables - Part II**

**Table 1:** Molecular Treatment of Gastric Cancer  
P.M. Hoff (Brazil)

**Table 2:** Molecular Treatment of Colorectal Cancer  
R. Riechelmann (Brazil)

**Table 3:** Molecular Treatment of Lung Cancer  
C. Mathias (Brazil)

18.10  End of the live educational workshop
Workshop faculty

Carlos L. Arteaga
Carlos Canela
Gabriela Cinat
Renata de Almeida Coudry
Bernardo Garicochea
Henry Gomez
Paulo Marcelo Hoff
Jorge León Chong
Hernán Lupera

Clarissa Mathias
Elizabeth Mickiewicz
José Miguel Reyes
Rachel Riechelmann
Clarissa Serodio Baldotto
Carlos Silva
Carlos Vallejos
Heinz Zwierzina
Dr. Arteaga obtained his MD degree at the University of Guayaquil in Ecuador. He trained in Internal Medicine and Medical Oncology at Emory University and the University of Texas Health Sciences Center San Antonio, respectively. He joined Vanderbilt in 1989 where he now holds the Donna S. Hall Chair in Breast Cancer Research and serves as Professor of Medicine and Cancer Biology. Dr. Arteaga is also Associate Director for Clinical Research and Director of the Breast Cancer Research Program of the Vanderbilt-Ingram Cancer Center (VICC). He is also the founding director of the new Center for Cancer Targeted Therapies at VICC. He has over 250 publications in the areas of signaling by growth factor receptors and oncogenes in breast tumor cells, development of targeted therapies and biomarkers of drug action and resistance and investigator-initiated clinical trials in breast cancer. Since 2002, he has directed the NCI-funded Vanderbilt Breast Cancer SPORE where he co-leads several investigator-initiated clinical trials. His research is funded by the National Cancer Institute, the American Cancer Society, the Department of Defense Breast Cancer Research Program, Stand Up 2 Cancer (SU2C) and the Susan G. Komen for the Cure and Breast Cancer Research foundations. He is a member of the American Society of Clinical Investigation (1998) and the Association of American Physicians (2005). He served as member of the Experimental Therapeutics-2 NIH Study Section (1998-2003), the NCI Board of Scientific Counselors (1999-2004), NCI Parent Subcommittee A for review of Cancer Centers (2004-2008), the Breast Core Committee of the Eastern Cooperative Oncology Group (ECOG), and the Board of Directors of the American Association for Cancer Research (2004-2007). He co-chaired the former Developmental Therapeutics Committee of ECOG and chaired the AACR Special Conferences Committee (2002-2008). Arteaga is the recipient of the 2003 AACR Richard & Hinda Rosenthal Award, a 2007-2017 ACS Clinical Research Professor Award, the 2009 Gianni Bonadonna Award from the American Society of Clinical Oncology (ASCO) and the 2011 Brinker Award for Scientific Distinction from the Susan G. Komen for the Cure Foundation. As of 2012, he serves in the Scientific Advisory Board of the Komen Foundation. He has chaired the AACR Special Conference ‘Advances in Breast Cancer Research’ since 2003 and has served as AACR co-chair of the annual San Antonio Breast Cancer Symposium since 2009. He is Deputy Editor of Clinical Cancer Research and member of the Editorial Board of Cancer Cell and six other peer-reviewed journals. He serves on the advisory boards of several academic cancer center-based Breast Cancer Programs and NCI-designated Cancer Centers. In 2013, he was voted by the AACR membership as President Elect of the American Association for Cancer Research.
Gabriela Cinat, M.D., is a certified Clinical Oncologist of the Clinical Oncology Department at the Angel H. Roffo Institute of Oncology, University of Buenos Aires in Argentina, at the Melanoma and Sarcoma Unit. Dr. Cinat obtained her medical degree in 1984 from the University of Buenos Aires. She subsequently completed a residency in clinical oncology at the Angel H. Roffo Institute of Oncology, University of Buenos Aires, Argentina. She heads the Department of Oncology at the Fundación CIDEA where she has been a principal investigator in many clinical trials focusing on melanoma, sarcoma, and cancer vaccines, and she has published national and international papers and book chapters. Dr. Cinat is a member of the Asociación Argentina de Oncología Clínica and the American Society of Clinical Oncology.

Carlos Canela G. graduated from the Universidad Nacional Autónoma de México in 1987. Thereafter, he completed his specialist training in internal medicine at the Central Hospital of IVSS Dr. Miguel Pérez Carreño in Caracas, Venezuela. Dr. Canela worked as a Medical Oncologist at the Dr. Luis Razetti Oncology Institute in Caracas, Venezuela, and is Deputy Medical Oncology Service, Clínica Santa Sofía, Caracas. Since 2011 Member of Board of directors of Venezuelan Anticancer Society. Dr. Canela’s clinical interest and expertise focuses on breast, lung cancer and head & neck.
Biographies

**Renata de Almeida Coudry**

Instituto do Câncer do Estado de São Paulo (ICESP)
Hospital Sírio Libanês
São Paulo, Brazil

Head of Anatomic Pathology and Medical Coordinator of Biobanking at the Sírio Libanês Hospital, she is supervisor at the Sírio Libanês Hospital and School Medicine of São Paulo, post-graduation programs.

Researcher in the field of gastrointestinal cancer and molecular biomarkers. She is an experienced Pathologist with more than 20 years working with Surgical Pathology.

She has more than 10 years of experience in Molecular Pathology, conducting molecular diagnostic tests and directing molecular facilities.

**Bernardo Garicochea**

Hospital Sírio Libanês
Centro de Oncologia
São Paulo, Brazil

Clinical Oncologist.

Professor of Internal Medicine – Pontifícia Universidade Catolica – Porto Alegre - RS- Brazil.

Director of the Oncology Department - Pontifícia Universidade Catolica – Porto Alegre - RS- Brazil.

Coordinator of the Oncogenetics Unit – Oncology Center- Hospital Sirio Libanes – SP.

Post Doc – Leukemia Biology – Royal Post Graduate medical School – London UK.

Post Doc – Human Genetics – Memorial Sloan Kettering Cancer Center - NY.
Henry Gomez
Division de Medicina
Instituto Nacional de Enfermedades Neoplasicas
Lima, Peru

Dr. Henry Gomez, Doctor of Medicine from the Universidad Peruana Cayetano Heredia, Master in Molecular Oncology CNIO Spain, Director of the INEN Medicine Direction, Associate Member of the National Academy of Medicine of Peru. His main interest is the clinical and translational breast cancer research, an area that has many publications and has won several awards.

Paulo Marcelo Hoff
Instituto do Câncer do Estado de São Paulo (ICESP)
São Paulo, Brazil

Paulo M. Hoff is Professor and Chairman of Medical Oncology at the University of São Paulo and General Director of the Instituto do Câncer do Estado de São Paulo, Octavio Frias de Oliveira. He is also the General Director of the Oncology Center at the Hospital Sírio Libanês in São Paulo, Brazil and member of Board of Directors of American Society of Clinical Oncology. Prior to this he was an Associate Professor and Deputy Chairman in the Department of GI Medical Oncology at the University of Texas, MD Anderson Cancer Center, TX, USA. Dr. Hoff was a fellow in hematology/oncology and chief fellow in medical oncology at the MD Anderson Cancer Center. He is a Fellow of the American College of Physicians, and has been granted a number of awards for achievement, including best research as a senior fellow, Merit Award from the American Society of Clinical Oncology (ASCO), Comenda do Alvorada from the Government of Brasília as well as being selected as one of America’s top physicians for several years.

Dr. Hoff’s research interests include the development of new antineoplastic drugs as well as treatment of gastrointestinal and neuroendocrine cancers, focusing on oral and molecular targeted agents. He has edited or co-edited more than 16 medical books and published more than 150 peer-reviewed articles as well as more than 100 books chapters. He is a member of several editorial boards, and is a member of many academic societies, including the Sociedade Brasileira de Oncologia Clínica (SBOC), the Sociedade Brasileira de Cancerologia (SBC), ASCO and the European Society for Medical Oncology (ESMO).
Biographies

Jorge León Chong
Oncosalud and
Instituto Oncologico Miraflores
Lima, Peru

Jorge León Chong obtained his medical degree at Universidad Nacional "Federico Villarreal" (Lima-Peru), and completed his residence in hemato/oncology at Instituto Nacional de Enfermedades Neoplasticas (INEN). Then followed a fellowship in high dose chemotherapy in solid tumors at service of Medical Oncology-Hospital "12 de Octubre" (Madrid-Spain) and master in molecular oncology at Centro Nacional de Investigacion Oncologica (CNIO), Spain.

He was attending phisycian at Oncologic Unit - Hospital Central PNP (Lima-Peru) and Department of Medical Oncology at INEN, where he was the Chief from 2007 to 2009.

Currently he is medical oncologist of Oncosalud and Instituto Oncologico Miraflores.

He was Project Manager of ECOG Peru and Associated Professor at Universidad Peruana Cayetano Heredia.

He is member of ASCO, ESMO, Sociedad Peruana de Oncologia Medica, Sociedad Peruana de Cancerologia and Sociedad Peruana de Mastologia.

Hernán Lupera
Hospital Metropolitano
Quito, Ecuador

Hernán Lupera obtained his medical degree at the Catholic University of Guayaquil in Ecuador, and completed his fellowship at the Institut Gustave- Roussy in Villejuif, France. Currently, he is an Oncologist of the Cancer Center at Metropolitano Hospital in Quito, Ecuador and Past President of the Ecuadorian Society of Hematology.

Dr. Lupera is also a founding member of several international societies such as the Andean Group for Investigation in Clinical Oncology (GAICO), the Ibero-American Coalition for Research in Clinical Oncology (CIBOMÁ), the Latino American Group of Clinical Research in Clinical Oncology (GLICO). He is also an active member of the American Society of Clinical Oncology (ASCO), the European Society of Clinical Oncology (ESMO), and the American Society of Hematology (ASH). In addition, Dr. Lupera has published over 25 original research articles and book chapters.
Clarissa Mathias obtained her medical degree at the Federal University of Bahia, Brazil. She then completed her residency in internal medicine at the Medical College of Pennsylvania, PA, USA, where she served as Chief Resident. She completed her hematology and oncology fellowship at the University of Pennsylvania. In addition, Dr. Mathias completed a PhD in internal medicine at the Federal University of Bahia in 2005. Currently, she is Medical Director at the Núcleo de Oncologia da Bahia in Brazil, where she is involved in several research protocols, and she is also the oncology coordinator at the Hospital Português.

Dr. Mathias is board certified in internal medicine, hematology and oncology by the American Board of Internal Medicine and in clinical oncology by the Brazilian Society of Cancerology. She is also a member of several societies such as the American Society of Clinical Oncology, the Brazilian Society of Cancerology and the Brazilian Society of Oncology, and has co-authored several peer-reviewed papers.

Elizabeth Mickiewicz is head of the Service of Clinical Oncology at the Instituto Angel H. Roffo, Universidad de Buenos Aires, Argentina, Director of the specialization in Clinical Oncology program, School of Medicine, Universidad de Buenos Aires.

Active member in the argentine oncology community; past president of the Asociación Argentina de Oncologia Clinica [A.A.O.C.] and current member of the advisory board of A.A.O.C. She has lectured intensively on urological and breast and lung cancer treatment, both in Argentina and neighbouring countries.

She has been an active member of ASCO and ESMO for many years.

Dr. Mickiewicz has coauthored over hundred 150 medical and scientific publications. She has been involved in several phase II and III chemotherapy and immunology treatment studies.

She is currently involved in molecular treatments.
José Miguel Reyes obtained his medical degree at the Universidad de Chile in 1978 and after that obtained his medical oncology degree at the same university in 1983. In 1985, he became Head of the Medical Oncology Department at the Hospital Paula Jaraquemada. Dr. Reyes moved to the Clínica Las Condes in Santiago to establish and direct the Oncology Department in 1991.

Dr. Reyes is the Head of the Prevention Department at Corporación Nacional Del Cáncer. His research interests focus on breast and GI tract tumors, and he has over 50 publications in these areas. He was the Medical Director of the Cancer Institute of the Clínica Las Condes until 2010. He is also an external advisor of the Chilean Ministry of Health since 2010.

He is associated professor of medical oncology at the University of Chile.

Rachel Riechelmann

Instituto do Câncer do
Estado de São Paulo [ICESP]
Oncology Department
São Paulo, Brazil

Dr. Rachel Riechelmann MD, PhD is a medical oncologist and clinical researcher in the field of Gastrointestinal Tumors. She is currently in charge of the Clinical Research Unit at the Cancer Institute of Sao Paulo, Sao Paulo, Brazil, and have several activities related to the education of oncology residents such as GI oncology and clinical research methodology. Dr Riechelmann also treats GI cancer patients at the Cancer Institute of Sao Paulo.

Her great passion is clinical research. She has an extensive experience in clinical trials methodology which she gained from her Clinical Research Fellowship at Princess Margaret Hospital, University of Toronto, Toronto, Canada, while working as a clinical research/medical manager at Novartis Oncology Pharmaceuticals, Brazil, and her my current position at the Cancer Institute. Her main research focus is on GI oncology, specifically colorectal cancer. Dr Riechelmann has more than 30 articles published in peer reviewed journals and has received several awards including three American Society of Clinical Oncology (ASCO) awards and a National Cancer Institute of Canada research grant in 2006.
Clarissa Serodio Baldotto
Instituto Nacional de Câncer
Rio de Janeiro, Brazil

Clarissa Baldotto is a Medical Oncologist in the Department of Clinical Oncology at Instituto Nacional de Câncer (INCA), Rio de Janeiro, Brazil. She also develops her activities at Clinical Research Department, as a clinical researcher fellow and coordinating clinical research educational program.

Dr. Baldotto’s main areas of interests include thoracic and central nervous system malignancies, focused on translational research. She is an active member of Multidisciplinary Thoracic Oncology Group at INCA and is finishing a master degree on thoracic oncology, specifically small cell lung cancer.

Dr. Baldotto is currently a member of the board of directors of Brazilian Society of Clinical Oncology (SBOC). In addition, she is a member of the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), International Society for the Study of Lung Cancer (IASLC), American Association for Cancer Research (AACR) and International Thymic Malignancy Interest Group (ITMIG). Recently she participated in the foundation of Young Oncologists group at SBOC and received the 2010 IDEA [International Development and Educational Award] from ASCO.

Carlos Silva
Hospital Británico de Buenos Aires
Buenos Aires, Argentina

Carlos Silva is Head of the Clinical Oncology Services of the Hospital Británico de Buenos Aires in Argentina, Head of Clinical Oncology Service of Hospital Universitario Austral and Profesor of Oncology of the Universidad Católica Argentina. Dr. Silva was trained in molecular oncology at the University of Buenos Aires, with additional specialty training in Europe and Latin America. He has served as an invited professor of clinical oncology and chemotherapy at the University of Salvador. He is the Director of the Annual Course on Molecular Biology of Cancer at the Universidad Católica Argentina.

Dr. Silva has participated in more than 20 clinical oncology studies as investigator or principal investigator. Ongoing trials include Phase II and III studies on treatments for NSCLC, breast cancer, colorectal cancer and melanoma. He has authored several national and international publications.

In addition, Dr. Silva received the LALCEC Quinto Centenario award and the Revista Médicos award for his community services in 2000 and the British Hospital Award in 2007. He is a member of the Society for Melanoma Research, the Asociación Argentina de Oncología Clínica, the Sociedad Argentina de Mastología, the Asociación Argentina de Ginecología Oncológica and of the Asociación de Oncología Clínica de la Provincia de Buenos Aires, and a former member of the Comisión Directiva de la Asociación Argentina de Oncología Clínica. He also is the scientific director of the Fundación CINO (Cuidado Integral del Niño Oncológico) and a former collaborator of the Fundación para la Investigación y Prevención del Cáncer (FUCA).
Carlos Vallejos
Chairman of the Latin American Education Council
Oncosalud
Lima, Peru

Dr. Carlos Vallejos Sologuren was the Institutional Chief of the Instituto Nacional de Enfermedades Neoplásicas (INEN), from February 2008 to January 2012 and he was Minister of Health 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 “European Society for Medical Oncology” (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); resides 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.

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

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 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
The idea of drugs acting like "magic bullets", with specific affinity for the harmful agent and no affinity for normal constituents of the body, goes back to 19th century, with Dr. Erlich. Since then our knowledge of cancer biology has grown fast, specially over the last 20 years. Information acquired about signal transduction and its relation, when altered, to carcinogenesis can be considered a milestone. Structural and functional alterations of the molecules involved in signal transduction have been observed in different tumor types and incorporated into clinical practice as therapeutic targets.

Over the last decade, the number of publications regarding cancer molecular biology and biomarkers has increased exponentially. And now we have probably identified most of the gene mutations, amplifications and rearrangements contributing to the rise and maintenance of most human cancers. Moreover we realize that these molecular changes are far beyond mutations. They also comprise complex new targets like tumor immunology, epigenetics and metabolic alterations. This paradigm shift was made possible by technologies and analytical tools developed and adapted to clinical research practice.

Progress is undeniable, but that are still considerable old and new issues challenging cancer translational research. Technology for genomic analysis is complex and bioinformatics tools lack standardization; new clinical trials designs are puzzling, often involving sophisticated biostatistics; real predictive biomarkers are hard to find in this huge amount of genomic information and regulatory agencies are not always prepared for these new advances. Along with all these issues, multidisciplinary collaboration has become more important and more complex than ever.

So now we know that cancer is a genomic disease based on reliable basic and clinical data. We have faced a turning point in oncology practice and there is no way back. This new genome era poses obstacles that must be circumvented in order to definitely incorporate precision oncology into clinical practice over the next years.
The movement of single cell organisms to more complex forms required many adaptations that in the last millions of years resulted in a complex and elegant machinery of communication. There is the necessity of interpreting the signals from the environment and from nearby cells in order the cells reduce or increase their metabolic rates and also to elicit division or apoptosis signals. Cell receptors have evolved to detect these signals. An extra-membrane domain detects the signal, generally provided by specific molecules, and the attachment of this ligand to the receptor works as a trigger that stimulates the receptor to horizontally moves into the membrane searching for a receptor partner, creating a receptor-dimer unit. Dimerization opens a chemically blocked region just inside the cytoplasm (the intracytoplasmic domain) resulting in the availability of multiple free tyrosine sites. Each tyrosine site is suitable for a limited number of proteins that are capable to attach to them through a chemical reaction involving phosphate exchange. These proteins known as tyrosine-kinases are them ready to generate an activation cascade involving a small number (but extremely complex) pathways. Many of these intermediary proteins can act as crossroads to other pathways. Using this intricate and redundant network, the cell can create different possibilities of signaling using a restricted number of proteins available in its nucleus and cytoplasm. Cancer cell, by definition, corrupt this well balanced system. Using the EGFR as a model to understand cell receptors, we will mention about the structural modifications that are involved in carcinogenesis. This model will help us to understand how receptors and their downstream signaling partners can be altered in multiple sites to generate a full malignant cell, how they can turn out to be interesting targets for treatment of different cancer, and their strategies to evade these new drugs.
The interaction between the cancer and the stroma, play a key role in the development of cancer. Metastases represent the end products of a multistep cell-biological process through angiogenesis, intravasation, and survival in the bloodstream, extravasation, epithelial-mesenchymal transitions (ETM) and metastatic growth. In this review, it takes emphasis in angiogenesis and ETM providing either biomarkers or potential drug targets

Angiogenesis is a pathophysiological hallmark, the expression of VEGF and other pro-angiogenic cytokines, which, in turn, stimulate endothelial cell proliferation. This leads to the formation of a highly abnormal tumor vasculature characterized by hyperpermeable vessels, increased vessel diameter, and abnormally thickened basement membranes. This abnormal vascular network also impair the efficacy of cytotoxic chemotherapy and radiation by enhancing tumor hypoxia and compromising intra-tumoral delivery of chemotherapy. The realization of potent angiogenesis inhibition can alter the natural history of tumors. However, in both preclinical and clinical settings, the benefits are at best transitory and are followed by a restoration of tumor growth and progression. Emerging data support a proposition that two modes of unconventional resistance underlie such results: evasive resistance, an adaptation to circumvent the specific angiogenic blockade; and intrinsic or pre-existing indifference.

Epithelial-mesenchymal transitions are events that convert adherent epithelial cells into individual migratory cells that can invade the extracellular matrix. Throughout evolution, the capacity of cells to switch between these two cellular states has been fundamental in the generation of complex body patterns. Cells undergo EMT to migrate and colonize distant territories. Not surprisingly, this is also the mechanism used by cancer cells to disperse throughout the body.
Treatment of cancer with surgery, radiotherapy, and chemotherapy has reached a plateau. New molecular target treatments are of increasing relevance as knowledge increases of different extracellular and intracellular fundamental pathways involved in the etiology and development of cancer processes. Immunology started many decades ago with interferon and interleukin-2, with the general intention of modifying the host response to the presence of a tumor as a foreign agent. I continue to have hope in the possibilities of curing cancer with minimal side effects, and immunising patients to prevent future cancers. In fact, we started working with irradiated whole melanoma cells in patients with advanced disease and bulky disease. The results were disappointing with no responses so far. We continued working in patients in the adjuvant setting and with more sophisticated vaccines but, again, results were disappointing and even discouraging.

Cancer is an immunogenic disease where several antigens can induce immune response. The response should be a cellular immune response and elicit a long-lasting immunologic memory. The immunological barriers are (i) the antigen should be widespread on cancer cells and should be well presented and processed by immune cells, many cancers have an enormous amount of antigen and many of them are shared for different tumors and normal cells at the same time; (ii) the host must be immunocompetent, and (iii) the tumor microenvironment should not inhibit immunoresponse, in fact, induced by tumor chemotactic properties, many cells from the immune system that normally present an inflammatory response such myeloid stem cells or macrophages are attracted to the site, inhibiting immune response. On the other hand, after a long inflammatory or tumor process, lymphocytes are exhausted are committed to dead by the actions of signaling pathways mediated by costimulatory molecules involved in two signal pathways such the PD1-PDL1 pathway. Several factors should however be taken into account; immunoresponse does not necessarily mean clinical effect.

There are several groups of antigens including non mutated (MAGE, BAGE, RAGE, NY-ESO), lineage specific (gp100, gp75, mda-7, tyrosinase, MART1/MELAN A), and epitopes derived from mutated genes (mutated Ras, mutated or wild type p53). The crucial point: is there a critical tumor-cell mass beyond which immunological treatments are futile?

There are different strategies using cellular immunotherapy (in vivo: BCG, gene modified cancer vaccines, recombinant cytokines, heat shock proteins, or ex vivo: peptide pulsed dendritic cells, dendritic cells transfected with tumor derived messenger RNA); non-specific immunologic stimulants; adoptive transfer; blockade of immunosuppressors (anti-CTL4); non T-cell-directed vaccines. Other vaccines include anti Her2/neu and several melanoma vaccines. Trials of these strategies will require uniform types of patients, significant patient numbers and an adequate length of follow up. But today the kings of molecules are those antibodies blocking immune check points such anti CTL4 and anti PD1 antibodies showing an unprecedented kind, amount and durability of response.

Finally, small molecules directed against selected molecular targets have been shown to have unexpected immunologic activities. A new approach combining such strategies is warranted.
The potential of cancer cells to evade immunological destruction has become one of the “hallmarks of cancer”. In most cancer patients, the activity of the immune system to attack the tumour is suppressed and immunomodulating agents aim to activate the patient’s immune system to fight cancer. Numerous novel therapeutic strategies have arrived in clinical research but so far mainly therapeutic antibodies have succeeded in phase III trials.

Monoclonal antibodies (moAbs) are IgG molecules, a human immune globulin class with specific binding domains in the variable region of the antibody. Several different mechanisms for moAbs to kill tumor cells via immune mobilization have been postulated. In antibody-dependent cell-mediated cytotoxicity (ADCC), native antibodies coupled to a cell surface antigen bind natural killer (NK) cells. This triggers localized discharge of lytic proteins (perforins) and granzymes (enzymes from granules within NK cells) that form pores in the cell membrane and induce osmotic swelling and cell lysis. Another principle of antibody action is complement-dependent cytotoxicity (CDC) that can also lead to the formation of cell membrane pores, osmotic swelling and cell lysis.

Recently, antibodies that target checkpoints of the immune system have arrived in the clinic. The CTLA-4 antibodies ipilimumab and tremelimumab are currently being tested in phase II and III trials in melanoma, and in phase II trials in other tumour types. Ipilimumab has already been approved for unresectable or metastatic melanoma.

It is important to note that our standard RECIST criteria do not apply to immunomodulatory agents. Antitumor responses may be characterized by short-term progression followed by delayed regression, and an important clinical characteristic of anti–CTLA-4 antibodies is that the duration of clinical responses and even stable disease is often quite prolonged.

In addition to CTLA-4, the programmed death 1 protein (PD-1) is another key immune checkpoint receptor expressed by antigen-activated T cells. Several agents targeting the PD-1/PD-L1/PD-L2 pathway are currently in clinical development. Six drugs are in phase I/ II (AMP-224, BMS-936559, MPDL-3280A, MK-3475, MEDI-4736, CT-011) and one in phase III (BMS-936558). The latter, also called Nivolumab, is a fully human IgG4 anti-human PD-1 blocking mAb with no known Fc function (ADCC, CDC). It has a high affinity for PD-1, and blocks the binding of both PD-L1 and PD-L2. Recently (ASCO 2013) it has been reported that combination therapy with ipilimumab and nivolumab led to durable tumor shrinkage in approximately half of patients with aggressive, advanced melanoma. The objective response rates in the combination trial were better than rates in monotherapy trials of each drug.

In the complex tumour-immune modulatory network not only the tumour and the immune system play a role but also blood vessels and other tumour environmental components. Bavxituximab is a chimeric monoclonal antibody directed against the membrane phospholipid phosphatidylserine. Phase II clinical trials of bavituximab monotherapy and in combination with chemotherapy in adults with refractory solid tumors have been completed and demonstrated encouraging data e.g. in advanced non-small-cell lung cancer.

As in targeted therapy in general, the challenge for developing immunomodulatory agents is the identification and investigation of clinical biomarkers that will help in defining mechanisms of action and resistance, monitor change in immune status (pharmacodynamics), predict which patients will have enhanced benefit/risk, and finally predict drug combination partners.
Abstract not available at the time of printing.
Biomarkers have been traditionally used in daily clinical practice in the context of oncology treatment. They allow us to give, for example, a prediction about how a patient should respond to a specific treatment.

Medical oncology treatment requires the use of as many tools as it is possible to refine the treatment of each individual patient. At the beginning the approach to chemotherapy was “one drug fits all”, but quickly we recognised that many patients did not benefit from a treatment but only suffered its side effects. The example of chemotherapy is also applicable to all drug therapies in medicine.

Now we need a way to determine the correct treatment for the specific patient at the appropriate time. This is where biomarkers come in.

In the 2000s, a global effort was started to find markers that could allow us not only to treat a specific patient correctly, but also to provide tools to facilitate the prevention and early diagnosis of tumor disease.

Since then thousands of papers have been published on this topic and it is impossible to try to review all of them.

In this talk we provide a critical overview of biomarkers and we review some commonly used in the big killer tumors such as breast, colorectal, and lung cancer. We also try to identify why currently biomarkers used in these diseases fail in the adequate prediction and prognosis of the course of the disease and the treatment results.

We finish with some insights about liquid biopsy and The Cancer Genome Atlas, and their potential as a different tools to facilitate the decision making process in oncology.
Biomarkers were recognized first in hematologic malignancies: Many decades ago surface antigens were discovered in the blood cells and also cytogenetic alterations associated to different hematologic malignancies (acute and chronic leukemias, myelodysplastic syndromes, lymphomas, etc).

Biomarkers demonstrated prognostic and or predictive values and let to a new form to study the hematologic malignancies that include clinical, morphological, immunophenotype and cytogenetic or molecular criteria.

Clinical implications of the biomarkers include:
1. To improve diagnosis.
2. Development of new classifications
3. Hematologic malignancies are stratified according to risk groups
4. Targeted agents were used in hematologic malignancies first , and the outcome of these patients are better now

In conclusion, in hematologic malignancies , biomarkers play role in:

a) Diagnosis  
b) Classification  
c) Prognosis  
d) Treatment
L9. New concepts in old targets: focusing on mechanism of resistance

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With the development of Molecular Oncology, many new families of drugs were synthesized using biotechnology. Using the new drugs, new side effects occur in the patients. Pathogenesis of these new side effects involves:

a) Infusion related events
b) Cytokine induced toxicities
c) Autoimmune toxicities

The most frequent side effects with the new drugs are:

1. Skin rash
2. Asthenia
3. Hand food syndrome
4. Diarrhea
5. Hypertension

Others less frequent but still important are:

1. Cardiomiophaty
2. Bleeding and thromboembolism
3. Interstitial pneumonitis
4. Infusion relates reaction
Neuroendocrine tumors are a group of tumors that could have different organ etiology.
Mainly they are classified as pancreatic and non pancreatic, and functioning and non functioning.
New classification and diagnostic procedures have given new insight about their treatment.
When we are in front of a functioning syndrome first step is to treat accordingly to it etiology. The use of somatostatine analogs (SSA) is the core treatment of the functioning syndromes. SSAs are not always efficient and we are expecting new drugs that could help us in this task.
The treatment of poorly differentiated, G3 tumors is the same we use for the treatment of small cell lung cancer, that means, the use of platinum based chemotherapy.
For the treatment of well or moderately differentiated neuroendocrine tumors we must separate them in pancreatic and non pancreatic tumors. Both benefit from the use of SSAs, that have been showed as cytotoxic as well as symptoms controlling products. The use of chemotherapy as well as other molecular treatment, apart from SSAs, is only indicated in pancreatic tumors. Bronchial tumors seems to be less sensitive to actual treatment strategies.
Squamous cell carcinoma of the head and neck (SCCHN) represents a challenging disease. Despite advances in surgery and radiotherapy, overall cure is achieved in less than 50% of patients. In contrast to other cancers, distant metastases are rarely present at diagnosis, but due to better local control, the incidence of systemic spread is rapidly increasing. On the other hand, at least two well-characterized diseases have been described in SCCHN, due to human papillomavirus infection and due to tobacco & alcohol abuse, but some patients have a mixed etiology. Over the last 10 years we have compiled evidence of distinct molecular characteristics of these two types of diseases by differences in mutational profiles, transcript level and epigenetics. HPV carcinogenesis involves significantly fewer genetic alterations and mutations than carcinogenesis independent of HPV (tobacco). Prospective phase III trials have reported differences in overall survival in HPV positive disease and HPV negative with differences of 30%. In absolute terms with any type of treatment given either radiation alone or combined modality treatment.

The most validated molecular target in HNSCC is EGFR. The monoclonal antibody cetuximab targets the EGFR extracellular domain and is associated with increased response and survival after platinum-based chemotherapy in metastatic or recurrent disease, and after radiation therapy for locally advanced disease. Nevertheless, the effects of EGFR inhibition in head and neck cancer have been modest in recurrent disease because over time patients develop resistance to this agent, and identify the mechanisms of resistance to EGFR inhibition might lead to strategies to overcome resistance, and could be an important source of novel targets for the treatment of HNSCC.

Some other promising drugs are under investigation for HNSCC, the irreversible EGFR/HER-2 inhibitor Afatinib is being compared head to head with cetuximab in a randomized crossover study. Due to its irreversible inhibition this compound remains active in many EGFR mutations, including the EGFRvIII mutation, which has been reported in HNSCC. Other novel strategies are studied to target EGFR, Sym004 represents a mixture of two IgG1 chimeric antibodies that target non-overlapping epitopes of EGFR domain III, this agent produces more rapid and efficient blockade and internalization with lysosomal degradation, and preliminary results are reported.

Despite more than a decade of study, many questions and unmet needs remain with respect to the use of EGFR inhibitors in HNSCC, foremost the need for predictive markers. Better understanding of mechanisms of sensitivity/resistance would greatly enhance patient selection and drug efficacy.
Molecular Treatment of Breast Cancer

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Molecularly defined disease subsets have been recently defined. Most melanomas have aberrations in signaling pathways that affect cell cycle progression, proliferation, and survival, including MAPK and PI3K pathways. Approximately 70% of melanomas carry mutations in at least 1 of 6 key genes, namely, *BRAF*, *c-KIT*, *NRAS*, *GNA11*, *GNAQ*, and *CTNNB1*. Tumors rarely have mutations in more than one of these genes. Each of these genes has one or more specific residues that are frequently mutated; however, some mutations are more common than others (e.g., *BRAF* V600 and *NRAS* Q61). The frequency of each mutation varies by tumor site and the presence or absence of sun damage. Approximately 80% of melanomas associated with intermittent sun exposure have mutated *BRAF* or *NRAS* 15%-20% of melanomas on mucosal, acral, and sun-damaged skin sites have mutated *c-KIT*. *GNAQ* is mutated in approximately 45% of uveal melanomas.

In many cases, tumor growth is also promoted by mutations in or excessive signaling through of RKT/GF receptors. These pathways include many oncogenes and tumor suppressor genes crucial to the development and progression of melanoma. Targeted therapies blocking each of these pathways at different points are under development, including *RTK/GFR* inhibitors, including imatinib, nilotinib, sunitinib, and dasatinib, that block *c-KIT*. Each melanoma tumor is characterized by the specific molecular aberrations present. Therapies under development should ideally be matched to those patients whose tumors rely on the pathway targeted by the inhibitor (i.e., “driver mutations”).

Vemurafenib and more recently dabrafenib are indicated for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* mutation. Approval was based on results from the phase 3 BRIM-3 and BREAK-3 clinical trials.

Current issues regarding *BRAF* and *MEK* inhibition include rapid response rates, but these are often short lived—recurrent tumors are often more aggressive.

*BRAF*-wild-type tumors may be stimulated by *BRAF* inhibition, therefore accurate assessment of *BRAF* status is critical.

Better understanding of resistance is needed to inform future sequencing and combination of targeted therapies. Over time, tumors exposed to *BRAF* inhibitors may actually become dependent on *BRAF* inhibition for growth and other mutations and pathways become drivers of tumor growth.

For *MEK* inhibitors, there appears to be limited single-agent efficacy in patients who progressed on prior *BRAF* inhibitor treatment. The combination of *BRAF* and *MEK* inhibitors are currently in development and may prolong resistance to single-agent therapy. The results of the phase 3 trials evaluating Dabrafenib+Trametinib vs BrAf inhibitors alone are eagerly awaited. Vemurafenib and the combination of Dabrafenib+Trametinib are currently being tested in the adjuvant setting.

Novel regimens of targeted therapies in combination with immunotherapy are currently undergoing clinical investigation.
Abstract not available at the time of printing.
Molecular Treatment of Colorectal Cancer

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In the last decade, several findings regarding the understanding of the molecular biology of non small cell lung cancer were incorporated to the knowledge of histologic type and staging. Some biomarkers have specific therapies that can personalize the treatment of patients.

Recently, the American College of Pathology, the International Association of Lung Cancer Study and the Molecular Pathology Association published guidelines to establish recommendations for the molecular analysis of lung cancer, necessary to guide therapies involving EGFR and ALK targets, determining which patients and samples should be tested and when the tests should be performed.

The Epidermal Growth Factor Receptors (EGFRs) stand at the origin of a major signaling pathway involved in cancer growth. Targeted therapies directed against EGFR are effective in a subset of non-small cell lung cancer (NSCLC) patients.

The IPASS study randomized 1217 patients with advanced NSCLC with adenocarcinoma histology who had never smoked or who had smoked very little. In these chemotherapy-naive patients, gefitinib was compared with the standard regimen of carboplatin and paclitaxel. Although overall survival did not differ between the 2 groups, progression-free survival at 1 year was superior in the gefitinib group (25% vs 7%; hazard ratio [HR], 0.74; \( P < .0001 \)). The IPASS study also found that patients with the EGFR mutation fared better with gefitinib than those without (overall response rate, 71.2% vs 1.1%). The North-East Japan trial (prematurely interrupted after interim analysis) and the WJTOG3405 trial demonstrated that treatment with gefitinib doubles the RR and significantly improves PFS as compared to chemotherapy. The first study with erlotinib as comparator was recently presented. In the OPTIMAL trial and the EUTARC trials, more recently presented, confirmed the benefits of EGFR tyrosine kinase inhibitors in selected lung cancer patients.

The EUTARC was a randomized phase III study performed in Europe in 174 patients diagnosed with metastatic adenocarcinoma, harboring EGFR mutations and treated with erlotinib or chemotherapy. The study reached its primary objective: improvement in median progression free survival 9.7 months in the group treated with erlotinib versus 5.2 months in the control group.

The LUX Lung 3 randomized patients harbouring EGFR mutation 2:1 to receive afatinib or pemetrexed/cisplatina. The response rate and progression free survival were higher in the group treated with afatinib.

Vascular endothelial growth factor (VEGF), which is an endothelial cell survival factor, is essential for the formation of new blood vessels, a process called angiogenesis. The ECOG 4599 study evaluated the incorporation of bevacizumab to a standard chemotherapy regimen. In addition to squamous cell carcinoma histology, the exclusion criteria included presence of brain metastases, clinically significant hemoptysis, and inadequate organ function or performance status. Median survival (primary end point) was longer (12.3 vs. 10.3 months) in the group assigned to chemotherapy plus bevacizumab, as compared with the chemotherapy-alone group (hazard ratio for death, 0.79; \( p = 0.003 \)). The median progression-free survival in the 2 groups was 6.2 and 4.5 months, respectively (hazard ratio for disease progression, 0.66; \( p < 0.001 \)), with corresponding response rates of 35% and 15% (\( p < 0.001 \)). Nintedanib, or BIBF-1120, is an oral anti-angiogenic drug studied in a phase III trial that randomized about 1300 patients to second line docetaxel alone to the same chemo with nintedanib and demonstrated a marginally significant improvement in PFS, but in patients with an adenocarcinoma, there was a much more striking improvement in PFS and OS.

The EML-4/ALK translocation is found in 2-7% of adenocarcinomas, more frequently in non smokers and not found in patients with EGFR mutations. The response rate in the PROFILE 1005 study was around 50% and in the A80811001 was 61%. These data led to approval of crizotinib in several countries. The phase III study randomized 347 patients who progressed after first line who had the EML4/ALK translocation to receive crizotinib or chemotherapy. Crossover was allowed. The progression free survival was 7.7 months in the group treated with crizotinib and 3 months in the group treated with chemotherapy. The response rate was 65% in the crizotinib arm and 20% in the chemotherapy group. no grupo de quimioterapia. These data confirm the indication of treating patients with EML4/ALK translocation with crizotinib.

Promising data on immunotherapy will be discussed in another lecture.

Targeting agents are becoming the standard of care in advanced disease. Clinical research related to these agents is primarily focused on patient selection for therapy, definition of predictors of response, and safety issues.
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