Advanced Clinical Trials Workshop China (ACT China)

国际临床研究高级研修班

18–20 November 2011
2011年11月18日至20日

Rose Manor
玫瑰庄园
## FRIDAY, 18 NOVEMBER

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<td>Co-chairs: Shukui Qin and Richard L. Schilsky (Room 201)</td>
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<tr>
<td>15:00–15:15</td>
<td>Welcome and introduction</td>
<td>Shukui Qin</td>
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<td>15:15–15:45</td>
<td>Ethical considerations in clinical trials</td>
<td>Sandra M. Swain</td>
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<td>15:45–16:00</td>
<td>Q&amp;A</td>
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<td><strong>Phase I clinical trials</strong></td>
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<td>16:00–16:45</td>
<td>Phase I clinical trials: objectives, design and endpoints</td>
<td>Lillian L. Siu</td>
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<td>17:15–17:45</td>
<td>Operating requirements for Phase I clinical trials</td>
<td>Jin Li</td>
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<td>18:00–18:30</td>
<td>Pharmacokinetics, pharmacodynamics, and identifying adverse events in Phase I clinical trials</td>
<td>Lillian L. Siu</td>
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<td>18:30–18:45</td>
<td>Q&amp;A</td>
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<tr>
<td>19:00–21:00</td>
<td>Welcome dinner</td>
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## SATURDAY, 19 NOVEMBER

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<td>Co-chairs: Yi-Long Wu and Sandra M. Swain (Room 201)</td>
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<tr>
<td>08:00–08:15</td>
<td>Welcome and housekeeping announcements</td>
<td>Yi-Long Wu</td>
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<tr>
<td>08:15–08:45</td>
<td>The principal investigator’s responsibilities in conducting clinical trials</td>
<td>Sandra M. Swain</td>
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<td>08:45–09:00</td>
<td>Q&amp;A</td>
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<td><strong>Phase II clinical trials</strong></td>
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<td>09:00–10:00</td>
<td>Objectives, design considerations and endpoint selection for Phase II clinical trials</td>
<td>Richard L. Schilsky</td>
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<td>10:00–10:15</td>
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<td>10:15–10:30</td>
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<td>10:30–11:00</td>
<td>Statistical considerations for Phase II trials and adaptive design</td>
<td>J. Jack Lee</td>
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<td>Biomarker-driven clinical trials</td>
<td>Yi-Long Wu</td>
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<td>Q&amp;A</td>
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<td>12:00–14:00</td>
<td>Lunch</td>
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<td>14:00–15:45</td>
<td>Simultaneous workshops:</td>
<td>Workshop co-chairs:</td>
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<td></td>
<td>1. Phase I clinical trial development</td>
<td>Lillian L. Siu</td>
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<td></td>
<td>(Room 202)</td>
<td>Jin Li</td>
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<td>2. Phase II clinical trial development in Lung cancer</td>
<td>Shun Lu</td>
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<td>(Room 203)</td>
<td>Yi-Long Wu</td>
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<td>3. Phase II clinical trial development in Breast cancer</td>
<td>Sandra M. Swain</td>
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<td>(Room 205-A)</td>
<td>Ze-Fei Jiang</td>
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<td>4. Phase II clinical trial development in Gastrointestinal cancers</td>
<td>Shukui Qin</td>
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<td>(Room 205-B)</td>
<td>Richard L. Schilsky</td>
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<td>15:45–16:00</td>
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<td>Co-chairs: Ze-Fei Jiang and J. Jack Lee (Room 201)</td>
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<td>16:00–16:30</td>
<td>Regulatory considerations</td>
<td>Frank Jiang</td>
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<td>16:30–16:45</td>
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<td>Phase III clinical trials</td>
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<tr>
<td>16:45–17:30</td>
<td>Phase III clinical trials: objectives, hypothesis and design considerations</td>
<td>Ze-Fei Jiang</td>
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<td>17:30–17:45</td>
<td>Q&amp;A</td>
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<td>17:45–18:15</td>
<td>Statistical issues in Phase III randomized clinical trials: interim analysis and data monitoring</td>
<td>Ning Li</td>
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<td>18:15–18:30</td>
<td>Q&amp;A</td>
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<td>19:00–22:30</td>
<td>CSCO gala banquet and social event</td>
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SUNDAY, 20 NOVEMBER

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<tr>
<td>08:00–08:10</td>
<td>Housekeeping announcements</td>
<td>Shun Lu</td>
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<td>Lillian L. Siu</td>
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<td>08:10–08:40</td>
<td>Lessons learned from Avastin® clinical trials in breast cancer</td>
<td>Sandra M. Swain</td>
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<td>08:40–08:55</td>
<td>Q&amp;A</td>
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<td>08:55–10:15</td>
<td>Reports from workshops (20 minutes each)</td>
<td>Nominated representatives</td>
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<td>10:30–11:00</td>
<td>Lessons learned from gefitinib and crizotinib clinical trials in NSCLC</td>
<td>Shun Lu</td>
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<td>Q&amp;A</td>
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<td>11:15–12:00</td>
<td>Summary panel discussion</td>
<td>Richard L. Schilsky</td>
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<td>12:00–12:15</td>
<td>Closing remarks</td>
<td>Shukui Qin</td>
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<td>Martin J. Murphy</td>
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On behalf of CSCO, STO and our Faculty, we extend our gratitude to Sanofi, our Charter Sponsor, who early on shared our vision for ACT China by providing strong encouragement and vital support.

We also extend our appreciation to Boehringer Ingelheim and Quintiles for their sponsorship and endorsement of ACT China.
DEAR COLLEAGUES,

On behalf of the Steering Committee, it is with great pleasure that we welcome you to the inaugural Advanced Clinical Trials Workshop China (ACT-China), held in partnership with the Chinese Society of Clinical Oncology (CSCO) and the Society of Translational Oncology (STO), USA. This workshop promises to be an exciting and enlightening one, with presentations and discussions which will provide insights into the essential elements of clinical trial excellence.

Clinical trials play a vital role in improving the outcomes of cancer patients as well as in the drug development process. They account for a significant proportion of total research and development expenditure. Pharmaceutical companies today face an ever growing demand from regulators and patients to expand their clinical trial programs. While there are clear benefits for the conduct of clinical trials in China, it is also acknowledged that there are several key issues concerning clinical trials in China which need to be addressed. It is important that steps be taken to align Chinese clinical trial standards with those used internationally as this will enable more Chinese cancer centers and their investigators to participate in more international studies. This is where ACT-China plays a crucial role.

In its mission statement, CSCO states that it is committed to developing continuing education and training programs for oncology professionals in China. Similarly, STO maintains a strong commitment to clinical trial excellence and both CSCO and STO are united in a common goal – the global fight against cancer.

Over the course of this 3-day workshop, an international and local faculty of experts will address the current issues and challenges in carrying out Phase I, II and III clinical trials through a series of lectures and discussions. We believe that the curriculum we have designed – covering ethics, preclinical studies, clinical trial design and conduct, statistics and regulatory considerations – will help transform oncology research in China for the benefit of cancer patients in China and around the world.

As part of our commitment to clinical trial excellence, it is our hope to deliver this program to a wider audience in the future and hence your active participation and feedback is most appreciated. We also appreciate the Charter Sponsorship of Sanofi Oncology and in particular the late Thomas Kelly who championed this CSCO cause from the outset. Sanofi's Charter Sponsorship is a testimonial to Tom and to his dedication to cancer patients. We are also thankful to Boehringer Ingelheim and to Quintiles for their sponsorship of ACT China-2011.

Last but not least, we hope that you will find this workshop meeting to be a rewarding and informative experience.
PROFESSOR SHUKUI QIN, a senior medical oncologist, is a Professor of Medicine and Chief Physician in the Medical Oncology Department, Vice President of Nanjing Bayi Hospital and Chairman of the Chinese PLA Cancer Center. He currently holds professorships at the Secondary Military Medical University in Shanghai, the Hangzhou Normal University, the Medical School of Chinese Nanjing Southeast University, the Oncology Teaching Office of the Nanjing Traditional Chinese Medicine University and Anhui Medical University. Professor Qin’s main focus is gastrointestinal cancers and liver cancers.

Professor Qin is the current President of the Chinese Society of Clinical Oncology. He is also Council Member of the Asia Clinical Oncology Society (ACOS), Senior Council Member of the Chinese Anti-Cancer Association (CACA), Vice-President of the National Committee for Cancer Palliative Therapy & Pain Control and Chair of the Liver Cancer Group of the National Ministry of Health, to name a few.

Professor Qin serves as Editor-in-Chief of the Journal of Chinese Clinical Oncology as well as The Oncologist (Chinese version). He is also an Associate Editor-in-Chief of the Chinese Clinical Oncology Year-Books, the Journal of Cancer Research and Clinical Oncology and The Chinese-German Journal of Clinical Oncology.

To date, Professor Qin has published more than 400 medical papers and 44 academic works. He has participated in more than 80 international multi-center clinical trials and 48 domestic clinical trials. Professor Qin is the recipient of the Special Talent Allowance of State Council and more than sixteen Chinese National and Provincial scientific awards for his outstanding contribution in academic and research fields.

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DR. RICHARD L. SCHILSKY is Professor of Medicine and Chief of the Section of Hematology-Oncology at the Department of Medicine at the University of Chicago. An international expert in gastrointestinal malignancies and cancer pharmacology, he has served on a number of peer review and advisory committees for the National Cancer Institute (NCI) including as a member and chair of the NCI Board of Scientific Advisors and as a member of the Clinical and Translational Research Advisory Committee.

Dr. Schilsky earned his M.D. at the University of Chicago Pritzker School of Medicine in 1975. He has previously served as Director of the University of Chicago Cancer Research Center (1991–1999) and as Associate Dean for Clinical Research (1999–2007). From 1995–2010, Dr. Schilsky also served as Chairman of the Cancer and Leukemia Group B, an NCI-sponsored national cancer clinical trials group.

Dr. Schilsky has served as a member of the Board of Directors of the American Society of Clinical Oncology (ASCO) and as ASCO President from 2008–2009. He presently serves as a Board member and secretary of the ASCO Conquer Cancer Foundation. He is a member of the external advisory committees of several comprehensive cancer centers including the Mayo Clinic Cancer Center, the MD Anderson Cancer Center and Duke University Comprehensive Cancer Center, to name a few.

Dr. Schilsky is Senior Associate Editor of Molecular Oncology, Associate Editor of Clinical Cancer Research and the Journal of the National Cancer Institute and a member of the editorial boards of EMBO Molecular Medicine, Cancer Prevention Research, Cancer Investigation, and Seminars in Oncology, among several other notable journals. He has published more than 290 articles and book chapters in the medical literature and is the editor of four books.
**PROFESSOR YI-LONG WU** is the President-Elect of the Chinese Society of Clinical Oncology, the past Director of the Chinese Society of Lung Cancer and current President of the International Chinese Society of Thoracic Surgery. A Fellow of the American College of Surgeons, he is also a member of the staging committee of the International Association for the Study of Lung Cancer and a member of the International Affairs Committee of the American Society of Clinical Oncology (ASCO). Professor Wu is Vice President of the Guangdong General Hospital and Guangdong Academy of Medical Sciences, and a director of the Guangdong Lung Cancer Institute.

Professor Wu's research focus is on multi-disciplinary synthetic therapy of lung cancer and evidence-based medicine in oncology. A regular figure at international lung cancer meetings, Professor Wu has presented on numerous topics ranging from Chinese lung cancer staging, neoadjuvant and adjuvant chemotherapy and targeted treatment data. Over the course of his career, he has been an invited speaker at numerous international lung cancer congresses, and chaired many national meetings.

Professor Wu has published more than 300 academic papers in peer-reviewed international and national journals. In addition, he has published 19 books and owns three invention patents. His achievements in the field have had a profound influence on the lung cancer profession in China.

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**DR. SANDRA M. SWAIN** has been elected to become President of the American Society of Clinical Oncology (ASCO). Dr. Swain took office as President-Elect during ASCO’s 47th Annual Meeting in June 2011 and will serve for a one-year term as President beginning in June 2012.

Dr. Swain is the Medical Director of the Washington Cancer Institute at Washington Hospital Center (WHC) in Washington, DC. She also serves on the Board of Directors for the WHC and WHC Foundation. Dr. Swain is a professor of medicine at Georgetown University and adjunct professor of medicine at Uniformed Services Health Science Center (USHSC). She previously served as the Deputy Director of the Medicine Branch and Chief of the Cancer Therapeutics Branch at the National Cancer Institute, National Institutes of Health (NIH).

Dr. Swain has led more than 20 clinical trials and published more than 180 articles in prestigious medical journals, including the *New England Journal of Medicine*, *Journal of Clinical Oncology*, *Clinical Cancer Research*, and the *Journal of the National Cancer Institute*. Her research focuses on adjuvant therapy for breast cancer and molecular targeted therapy for advanced and inflammatory breast cancer.

Since becoming a member of ASCO in 1986, Dr. Swain has demonstrated a strong commitment to the Society with her involvement in numerous ASCO committees including the Program Committee, Ethics Committee, International Affairs Committee, Finance Committee, and Strategic Planning Committee. She has held various leadership roles serving on the Board of Directors for ASCO and Conquer Cancer Foundation of ASCO, and serving as Chair of the Cancer Education and Nominating Committees.

Dr. Swain is the Breast Committee Vice-Chair and serves on the Board of Directors for the National Surgical Adjuvant Breast and Bowel Project. She has been honored with a Mentor of Merit award as a Distinguished Clinical Teacher at the NIH, and has been named one of the Best Doctors in America by *Good Housekeeping* magazine and a “Top Doctor” by *Washingtonian* magazine.
**DR. JIN LI** is a Professor and Dean of the Department of Medical Oncology at the Fudan University Cancer Hospital, Shanghai. Dr. Li is also the Director of the Clinical Trials Unit at Fudan University Shanghai Cancer Center and the current Secretary General of CSCO.

A practicing physician for the past 29 years, Dr. Li specializes in the treatment of gastrointestinal cancers. He has participated in approximately 100 clinical trials for the treatment of various tumor types including more than 10 global trials since 2004. Dr. Li was lead investigator on 12 Phase I studies, the development of S1 for the treatment of gastrointestinal cancer in China, and the development of an original novel agent (Apatinib), which is currently moving forward to Phase III clinical trials.

Dr. Li has been responsible for approximately 12 investigator-initiated research projects including the development of a carcinoembryonic antigen vaccine for the treatment of gastrointestinal cancer, and several translational studies involving biomarker identification through the correlation of clinical response with collected patient specimens and/or pharmacodynamic changes on magnetic resonance imaging. He has published in numerous journals including the *European Journal of Cancer*, the *Journal of Gynecologic and Obstetric Investigations*, the *Journal of Clinical Gastroenterology* and the *Chinese Journal of Oncology*.

**DR. J. JACK LEE** is the incumbent of the John G. & Marie Stella Kenedy Foundation Chair in Cancer Research Professor of Biostatistics, Department of Biostatistics, Division of Quantitative Sciences, MD Anderson Cancer Center. He holds joint appointments as Adjunct Professor of Statistics, Rice University, Houston, Texas; Adjunct Professor of Biostatistics, University of Texas School of Public Health, Houston; and Regular Member of the Graduate Faculty, Graduate School of Biomedical Sciences, University of Texas Health Science Center, Houston. In addition to many learned societies he is a member of the board of directors or the International Chinese Statistical Association.

He is the principal designer of the pace-setting BATTLE clinical trial that links potential biomarkers to drugs for lung cancer. This biopsy-based study tilts the field toward personalized treatment and more efficient clinical trials.

**DR. ZEFEI JIANG** is a Professor of Medical Oncology and Director of the Breast Cancer Department at 307 Hospital Cancer Center at the Academy of Military Medical Sciences, Beijing.

A Consultant of the State Food and Drug Administration (SFDA) and a standing committee member of the Chinese Society of Clinical Oncology and the Drug Information Association, Dr. Jiang is also a member of the St. Gallen International Breast Cancer Experts Consensus Panel.

Dr. Jiang has vast experience in clinical research and has been a principal investigator in various local as well as international clinical studies. He is actively engaged in research and clinical trials relating to breast cancer and has published over 150 papers in journals locally and abroad.
DR. LILLIAN L. SIU is a Senior Staff Physician in the Division of Medical Oncology and Hematology at Princess Margaret Hospital, Toronto, and a Professor of Medicine at the University of Toronto. Dr. Siu is Director of the Phase I Program and Co-Director of the Robert and Maggie Bras and Family Drug Development Program at Princess Margaret Hospital.

Dr. Siu’s major research focus is in the area of new anticancer drug development, particularly with respect to phase I trials and head and neck malignancies. She is the principal investigator of a phase I cooperative agreement U01 award (2008–2013) sponsored by the United States National Cancer Institute, which aims to expedite the access and evaluation of novel anticancer agents.

Dr. Siu is the recipient of national and international awards such as the Elsie Winifred Crann Award from the University of Toronto in 2001 and the Michaele C. Christian Award in Oncology Drug Development from the US National Cancer Institute in 2010. Internationally, Dr. Siu has been a member of the AACR International Membership Committee, the ASCO Head and Neck Cancer Scientific Program Subcommittee, and the EORTC Protocol Review Committee. Dr. Siu was the Neuroendocrine Tumor Task Force Chair in the North American Gastrointestinal Intergroup Scientific Steering Committee from 2007–2009; and she was the ASCO Grants Selection Committee Chair in 2009–2010. In 2009, Dr. Siu was awarded a Cancer Care Ontario Tier 1 Chair in Experimental Therapeutics. Dr. Siu has a strong background in clinical trial methodology and has been a member of the Program Committees for both the ECCO/ASCO/AACR workshop in Flims, Switzerland and the AACR/ASCO workshop in Vail, Colorado. Dr. Siu has published over 110 peer-reviewed manuscripts, and she is currently on the Editorial Boards of Journal of Clinical Oncology, European Journal of Cancer, and Cancer Discovery.

DR. SHUN LU is a Professor at the Shanghai Chest Hospital at Jiao Tong University and he is the current Chief of the Shanghai Lung Cancer Center. Dr. Lu’s dedication to the field is demonstrated by his active involvement in many oncological societies, both locally and abroad. He is a member of the American Clinical Oncology Society and Multidisciplinary Cancer Management Course Working Group; and the International Association for the Study of Lung Cancer.

Dr. Lu is a member of the Expert Panel of the State Food and Drug Administration of China, Commissioner of the Oncology Society of the Chinese Medical Association, Deputy Secretary of the Chinese Society of Clinical Oncology, Vice Director of the Chinese Lung Cancer Study Association and Commissioner of the Cancer Rehabilitation and Palliative Treatment Society Chinese Anticancer Association, among several others. Dr. Lu is also an Associate Editor of the Journal of Thoracic Oncology.

Dr. Lu’s major research focus is in the area of novel targeted agents, particularly with respect to lung and other thoracic tumors. He has served as principal or co-principal investigator of several international clinical trials and has more than 60 papers to his name, published in journals such as the Journal of Thoracic Oncology, Current Therapeutic Research, Oncology Reports and Diseases of the Esophagus, to name a few. Dr. Lu is the recipient of several notable awards including the New Medical Star in Shanghai award which he received in 2002 and 2004. In 2010, Dr. Lu was honored with the Shanghai Outstanding Medical Academic Leader award.
DR. NING LI is the Head of Regulatory and Medical Policy in Sanofi Asia and China.

Prior to his current assignment, Dr. Li worked at the US Food and Drug Administration (FDA) for more than 12 years as a regulatory reviewer. Whilst at the FDA, he has held the positions of reviewer, senior reviewer, team leader and branch chief responsible for the areas of oncology and cardiovascular products.

Prior to joining the FDA, Dr. Li was based at the Department of Internal Medicine at the University of Iowa; and at the Westat-NIH AIDS Clinical Trials Coordinating Center. He has been an adjunct faculty member at the Johns Hopkins University since 2008. Since 2010, Dr. Li has served as a member of the Drug Information Advisory Council of China.

Dr. Li obtained his medical degree from Shanghai First Medical College (Fudan University) and his doctorate from the University of Iowa. To date, he has published more than 30 scientific papers in the area of clinical trial methodology.

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DR. FRANK JIANG is the Vice President and Head of Asia Pacific Research and Development (R&D) for Sanofi.

Dr. Jiang is a Physician by training and has a PhD in Immunology. He joined sanofi-aventis in 2002 as a Clinical Research Director. In 2006, Dr. Jiang moved to Shanghai as the Head of China Clinical Research Unit for Sanofi. In 2008, he was appointed Vice President and Head of China R&D and in 2010, Vice President and Head of AP R&D.

Dr. Jiang holds a clinical professorship in Internal Medicine at the Robert Wood Johnson Medical School in New Jersey, where he is licensed.

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DR. MARTIN J. MURPHY, JR has four decades of healthcare and cancer research, extensive experience as a peer-reviewed cancer scientist, is a Professor of Medicine, editor and oncology consultant. Dr. Murphy, a graduate of New York University, was awarded postdoctoral fellowships at the Institut de Pathologie Cellulaire, Paris, France, the Patterson Laboratories of the Christie Hospital and Holt Radium Institute, Manchester, UK, and the John Curtin School of Medical Research, Australian National University, Canberra, Australia. He was on the faculty of St. Jude Children's Research Hospital, Memphis, TN, Memorial Sloan-Kettering Cancer Center, New York, NY and Wright State University School of Medicine, Dayton, OH. Dr. Murphy founded the Hipple Cancer Research Center in 1977 and led it for the next two decades as its chief executive officer. Endeavouring to advance new discoveries and enhance improved global healthcare delivery, Dr. Murphy founded AlphaMed Consulting, and for more than fifteen years has provided support for comprehensive cancer centres as well as selected cancer research-intensive pharmaceutical and biotech companies.

Dr. Murphy is convener and co-chair of ACT-China, and member of the National Cancer Policy Forum of The Institute of Medicine (IOM) of the National Academy of Sciences in the US. He is chairman of The Conquer Cancer Foundation of the American Society of Clinical Oncology, a director of the Foundation for the National Institutes of Health, and a charter member and director of C-Change founded by former President George H. W. Bush and former First Lady Barbara Bush. Dr. Murphy is founding chief executive officer of the CEO Roundtable on Cancer, established in 2001 at the request of former President George H.W. Bush. He and Ann Murphy, PhD, were married in 1965; they have five children and 10 grandchildren.
Ethical considerations in clinical trials

Sandra M. Swain

This is an overview of the ethical principles and regulatory aspects of biomedical research in the United States. The advances of biomedical research over the past century have resulted in the conquering of many diseases and an improvement of the quality of life for many. Researchers have an undeniable power to impact health status with the development of vaccines, new drugs and devices. The manner in which this is achieved has raised questions over the years and necessitated that a code of ethics be developed and implemented.

This presentation introduces the concepts of biomedical ethics as they apply to conducting research on human subjects. It also discusses regulatory requirements relevant to research conducted in the US. Included is an overview and explanation of the Belmont Report, which provides the three main principles of ethical conduct. The application of these principles is explained in the context of common practices. The processes of informed consent and the selection of human subjects are discussed as key components of ethical conduct and direct application of the Belmont Principles. An example of current ethical dilemmas is also presented to illustrate the ethical questions and challenges faced by researchers involved in human subjects research.

Phase I clinical trials: objectives, design and endpoints

Lillian L. Siu

Phase I clinical trials represent the first evaluation of a new drug or drug combination in humans and lay the foundation for a successful drug development process. The primary objective of Phase I trials is to define drug safety, tolerability and dose-limiting toxicities (DLT) in order to recommend an appropriate dose for subsequent Phase II trials (recommended Phase II dose [RPTD]). The secondary objectives are to characterize the pharmacology of the drug including pharmacokinetics (PK) and pharmacodynamics (PD) and to examine for preliminary evidence of antitumor activity. In this session, the fundamental elements of Phase I trials will be discussed, including selection of a starting dose and eligibility criteria. While the key guiding principle behind each of these Phase I trial elements remains focused on defining the safety of a new drug or drug combination, the emergence of the molecularly targeted era has led to specific considerations and these will be highlighted using examples. An overview of rule-based versus model-based dose escalation schemes, as well as their advantages versus limitations will be presented. The utilization of expansion cohorts to identify target patient populations of interest and/or to perform PD studies to demonstrate target engagement will be discussed. Phase I trial of drug combinations can be complex and thus will only be briefly described. At the end of this session, the participants should be familiarized with the basic concepts of Phase I trials and also appreciate some of the evolving complexities with dose-finding evaluations in early drug development.

KEY MESSAGES

- The primary objective of Phase I trials is to define a safe and tolerable dose of a new drug or drug combination that is appropriate for subsequent Phase II evaluation. Typically a pre-specified frequency of DLT is accepted and this specification helps to estimate the RPTD.
- Secondary objectives are to characterize pharmacology (what the body is doing to the drug = PK; and what the drug is doing to the body = PD) and preliminary antitumor activity.
- Rule-based and model-based dose escalation methods exist with relative advantages and limitations to derive at the RPTD. The underlying principle is consistent with any dose escalation methods: starting dose should be safe, escalate rapidly in absence of toxicity and escalate conservatively in presence of toxicity, minimize patients at low, potentially sub-therapeutic dose levels and treat more patients at higher, tolerable and potentially more therapeutic doses.
- The emergence of molecularly targeted agents has led to specific considerations for many elements such as eligibility criteria and definition of DLT in Phase I trials because of their on-target and off-target effects.

Operating requirement for Phase I clinical trials

Jin Li

In this presentation we will review the principles of construction of a Phase I unit, and the basic needs for creating a qualified Phase I team. An understanding of the infrastructure of a Phase I unit is critical in any center which is dedicated to Phase I trial design or study. This seminar will illustrate the issues around the regulatory needs of Phase I clinical trials, including pharmacokinetic analysis and bioequivalence evaluation. Compared with the late stage of clinical study, Phase I clinical trials are riskier for the subjects recruited, especially for those cancer patients with previous heavy chemotherapy. The Phase I team should be well-trained with experience in clinical studies, and be familiar with the process of working in a Phase I team.

KEY MESSAGES
After this presentation you should:

• Be familiar with the Phase I process.
• Be able to clearly define the infrastructure of a Phase I unit.
• Understand the basic needs of setting up a Phase I team.
• Understand the regulatory issues of conducting Phase I clinical trials.

REFERENCES:
Pharmacokinetics, pharmacodynamics, identifying adverse events in Phase I clinical trials

Lillian L. Siu

The collection, analysis and correlation of pharmacokinetic (PK), pharmacodynamic (PD) and safety data in Phase I clinical trials enables the comprehensive characterization of the pharmacologic and biologic properties of a new drug or drug combination. There are many ways in which PK results can contribute to the development of a new drug: i) stop dose escalation due to PK futility; ii) assist with dosing schedule determination; iii) help to explain toxicities encountered and/or PD effects observed; and iv) provide drug–drug interaction information. In Phase I trials, the conduct of correlative studies (such as assaying for PD effects in paired fresh tumor biopsies procured before treatment and during treatment) can provide guidance on the optimal biological dose especially if limited toxic effects are encountered during dose-finding. Furthermore, with an increasing number of compounds entering first-in-human testing, there are emerging interests and growing demands to demonstrate proof-of-mechanism (e.g. tumor shrinkage, stabilization of previously growing disease, target engagement in tumor tissues) as early as possible, e.g. at the completion of Phase I trials, such that agents with limited potential to ever succeed will be discontinued from further development. In Phase I trials, given the heterogeneity of the patient population enrolled, the lack of a control group, and the variability in drug dose or schedule among patients, it is not possible to validate the value of predictive biomarkers to identify those most likely to respond. However, the evaluation of companion diagnostic biomarkers that accompany the development of a new drug should begin from preclinical and early trial phases and may ultimately expedite its overall duration from first-in-man testing to approval. For safety assessments, standard terminology criteria for grading of adverse events exist to promote medical accuracy and consistency in data sharing and reporting. Toxicity pattern recognition and the careful assessment of acute toxicity in Phase I trials by experienced clinical teams help inform important safety signals with novel agents. The limitations of Phase I trials in capturing rare, late or cumulative toxicities will be discussed.

KEY MESSAGES

• PK parameters such as peak concentration (Cmax), exposure (area under time x concentration curve), half-life, clearance, etc. provide information about a drug’s pharmacologic properties. PK evaluations in Phase I trials provide the opportunity to optimize dosing schedule, understand drug–drug interactions and explain toxicity and PD effects observed.

• PD biomarkers provide information about the mechanistic effect of a therapeutic intervention on the patient and/or tumor.

• Predictive biomarkers cannot be validated in Phase I trials but the development of companion diagnostic biomarkers should occur early on to help elucidate the efficacy and/or safety of a specific drug for a targeted patient group or subgroups.

• Phase I trials provide the first evaluation of the safety profile of a new drug and it is important for experienced clinical teams to recognize toxicity patterns, perform careful assessments and report using standardized terminology criteria.

The principal investigator’s responsibilities in conducting clinical trials

Richard L. Schilsky

This presentation will summarize the responsibilities of the principal investigator (PI) of a clinical trial. Types of human subjects research will be reviewed and a definition for ‘clinical trial’ will be provided. The key elements of Good Clinical Practice (GCP) that specify the responsibilities of a study PI will also be reviewed. Foremost among these is that the PI is responsible for the overall conduct of the study, including: interactions with regulatory agencies, financial and regulatory aspects of the contract and/or grant that support the study, modifications to the original protocol submission, Institutional Review Board correspondence, other regulatory agency correspondence and the recruitment, training and supervision of the team running the trial. The PI may or may not also function as the sponsor of the study. The study sponsor is responsible for implementing and maintaining quality assurance for the trial in compliance with the protocol, GCP and regulatory requirements. These include developing the investigational plan, the manufacture and labeling of investigational products, obtaining regulatory approval before the study begins, initiating, suspending, or terminating the study as required and refraining from commercialization of the investigational product until regulatory approval is obtained. Quality assurance and managing potential conflicts of interest are essential to ensure the integrity of the trial and to maintain the public trust in the study results. The study PI should have access to all raw study data and should be independent in the analysis, interpretation and reporting of the study results.

KEY MESSAGES

• Compliance with international standards for GCP provides the foundation for effective and ethical conduct of clinical trials.

• The PI may delegate responsibilities to trained and qualified members of the research team but retains ultimate responsibility for all aspects of study conduct.

• Study monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, GCP, and the applicable regulatory requirements. Study auditing is a systematic and independent examination of trial related activities and documents to determine whether they adhere to the protocol, GCP, and the applicable regulatory requirements.

• The PI should have full access to the raw study data and control over how the data are analyzed and reported.

• Disclosure of financial or other interests, which might be construed as resulting in an actual, potential, or apparent conflict, is important to maintain the confidence of physicians, patients and the general public in the integrity of clinical cancer research.
Objectives, design considerations and endpoint selection for Phase II clinical trials

Richard L. Schilsky

Phase II clinical trials are an essential aspect of drug development that enables the “go-no go” decision to be made in order to advance a new agent to Phase III testing. The primary goals of Phase II trials are to estimate drug activity, describe toxicity, develop pharmacokinetic-pharmacodynamic (PK-PD) correlations, and confirm drug-target interactions. This presentation will review the essential elements of a Phase II trial including development of the primary objective and selection of the primary study endpoint, choice of the study population and description of the intervention to be studied. With the increasing number of targeted agents in clinical development, there is increasing use of time to event endpoints in Phase II clinical trials. The pros and cons of such endpoints will be described. Controversy exists regarding the relative merits of single arm and randomized Phase II trial designs. Examples of such designs will be provided and the circumstances in which each type of trial might be preferred will be described. Enrichment designs, such as biomarker-driven clinical trials and the randomized discontinuation design, provide opportunities to enrich the study population with individuals most likely to benefit from the treatment or to display the endpoint of interest. The merits and liabilities of such study designs will be described. At the conclusion of this presentation, participants should have an in-depth understanding of the design options for Phase II trials and should be able to select the optimal design based on the characteristics of the drug being studied, the clinical hypothesis being evaluated and the patient population being enrolled.

KEY MESSAGES

• The goals of Phase II trials are to estimate activity, describe toxicity, develop PK-PD correlations and confirm drug-target interactions.

• The optimal trial design will depend on the patient population being studied, the primary endpoint selected, the level of activity of interest, the precision of the estimate of activity.

• Assessment of disease progression depends on definition of progression and extent and frequency of evaluation but is always an estimate as true progression occurs between observations.

• Randomized Phase II designs reduce selection bias, improve patient comparability, and are generally preferred for progression-based endpoints and when historical data are unavailable or unreliable.

Statistical considerations for Phase II trials and adaptive designs

J. Jack Lee

The primary objectives of Phase II studies are to provide an initial assessment of a drug's efficacy (Phase IIA), refine a drug's toxicity profile, and compare efficacy among active agents to send the most promising one(s) to Phase III trials (Phase IIB). After the toxicity profile of an anticancer treatment is determined, Phase II studies are conducted to evaluate whether the new agent has sufficient anticancer activity to warrant further development. Statistical properties of clinical trial designs including Type I and Type II errors, P value, and Bayesian paradigm are briefly reviewed.

Typically, a Phase IIA trial is a single-arm, multi-stage study with a goal to screen out ineffective drugs. A sample size can range from 30 to 60 patients. The primary endpoint is often the clinical response. Commonly used designs include Gehan's design, Simon's two-stage designs, Ensign, et al. and Chen's three-stage designs, etc. In addition, Fleming's two-stage design allows for early stopping due to futility or efficacy. Bryant and Day's two-stage design monitors efficacy and toxicity simultaneously. Lee and Liu's predictive probability design allows continuous monitoring to increase the efficiency, flexibility, and robustness of trial conduct.

If an agent passes the Phase IIA evaluation, the subsequent Phase IIB trial is often a randomized, multi-arm study comparing effective treatments with a goal of identifying the most promising treatment regimen to evaluate further in a Phase III trial. The challenge is to choose the most promising regimens among a large number of potentially active regimens for further development.

In a review of randomized Phase II studies, Lee and Feng found that many studies applied randomization to achieve patient comparability, while embedding a one-sample Phase II design within each treatment arm. Due to limited sample sizes, such designs typically do not yield sufficient statistical power for a strict head-to-head comparison between treatment arms. Simon, Wittes and Ellenberg's pick-the-winner design has also been used. However, this ranking and selection procedure controls only Type II errors. As a result, the false positive rate can be high.

Randomized discontinuation design is suitable for cytostatic agents without known biomarkers. Seamless Phase II/III design speeds up the drug development by eliminating the “white space” between the two phases.

Bayesian adaptive designs are useful for learning and discovery. Response adaptive randomization, early stopping for futility and/or efficacy, add/drop agents are the most important features for adaptation. An example of the BATTLE trial in the development of targeted agents in lung cancer is given. Randomized Phase IIB studies are often designed with a moderate sample size (e.g. 50 to 200), a medium study duration (e.g. one to three years), and Type I and Type II error rates of 10% to 20%. A false positive result is of less concern because the final verdict of the effectiveness of a regimen can be provided in a Phase III evaluation. In addition, in order to shorten the study duration, earlier endpoints such as time-to-recurrence, disease-free survival, or time-to-progression are commonly employed in Phase IIB settings. A moderate to large expected difference is often assumed for Phase II studies. Comprehensive overviews on the design and analysis of Phase II cancer trials can be found, for example, in papers by Mariani and Marubini, Scher and Heller, and Gray, et al.

KEY MESSAGES
• Single-arm Phase IIA trials provide an effective way to assess the initial efficacy of new treatments.
• Multi-stage designs increase the study efficiency while the predictive probability design is more flexible.
• Pick-the-winner designs do not control Type I error.
• Interim monitoring and early stopping for futility of efficacy is desirable.
• Adaptive randomization enhances the study’s individual ethics.
• Bayesian adaptive design – learn as we go – is sensible and ideal for clinical trials.
• More randomized Phase II trials need to be conducted to screen out non-promising drugs/markers before launching Phase III trials to maximize the success rate.


Biomarker-driven clinical trials
Yi-Long Wu

The use of biomarkers in drug development clinical trials facilitates optimization of pharmacokinetic, pharmacodynamic and therapeutic properties thus enabling the best agent to be selected for clinical evaluation. To date, many targeted therapy agents for cancer have faced disappointing results when tested in clinical trials. In order to facilitate successful and efficient transition of a compound through the drug development pipeline, it is important to incorporate analytically validated and clinically validated biomarkers into rationally designed hypothesis-testing clinical trials.

The current challenges being faced in clinical trials today include the limitations of current biomarkers and imaging agent development methodologies, particularly for the molecular analysis of small tissue specimens, as well as regulatory and reimbursement policies. One of the issues faced in biomarker discovery is the availability of tissue samples for molecular analysis. In lung cancer for example, tumor tissue for molecular analysis is readily obtained through surgical resection in the early stages of the disease, but less frequently and only as small core-needle biopsies in advanced and treatment-refractory tumors. Molecular imaging of novel biomarkers or targets can add valuable spatial dimension and temporal data that could substantially improve assessments of targeted treatment efficacy. One successful example is the use of fluorodeoxyglucose and fluorothymidine positron emission tomography for the early prediction of nonprogression in advanced non-small cell lung cancer following erlotinib therapy.

Chinese researchers today face several barriers in biomarker discovery most notably regulatory issues, human subject protection issues, intellectual property issues, a lack of funding and resources, a fragmented infrastructure and a shortage of trained investigators.

KEY MESSAGES
• Biomarker-driven clinical trials are important to facilitate successful transition in the drug development pipeline.
• It is essential that the new generation of clinical trials stress the importance of biopsies to obtain relevant tumor specimens and the use of novel statistical designs to improve trial efficiency and treatment outcomes.

Regulatory considerations

Frank Jiang

Although there are no formal State Food and Drug Administration, P.R. China (SFDA) requirements or regulations that are specific for developing new oncology drugs, the special review and approval procedure can be used to support a consultation meeting prior to submission of CTA/NDA and shorten review time (to 80 days). SFDA may reduce their requirements for some oncology drugs including fewer patients and lower type 1 error. However, the requirements for biologics are much more stringent than small molecules.

Experience with sorafenib indicates that SFDA will focus on reducing drug lag where medical need is high in China. SFDA prefer overall survival as the primary endpoint for pivotal studies and mostly follow US regulatory and ICH guidelines. Only drugs approved in China for the indication under investigation can be used as comparators when comparing a new treatment with the standard of care. This can limit the opportunity for China to participate in a global trial. Biomarkers that support individualized medicine are increasingly important to optimize the benefit-risk ratio.

Some specific situations require special consideration in China such as the impact of concomitant traditional Chinese medicines during a trial and limitations in exporting patient samples.

In summary, the Chinese regulatory system for oncology drugs/trials is evolving, although with challenges. The rising bar for new drug approval calls for the understanding of regulatory requirements in the design and implementation of oncology trials in China. There is a huge need to develop regulations/guidelines for orphan drugs/early development for oncology drugs in China.

KEY MESSAGES

• Global trials (often conducted within Asia) are the most frequent registration strategy for imported drugs.

• Many of the principles of oncology drug development in US and Europe will apply in China although some considerations, such as choice of comparator, may be specific to China.

• The regulatory environment for developing new oncology drugs continues to evolve rapidly; personalized medicine is becoming increasingly important.
Phase III clinical trials: objectives, hypothesis and design considerations

Ze-Fei Jiang

Phase III trials are conducted in large patient populations (typically, the number of subjects range from 1,000 to 3,000). They can either be controlled or uncontrolled, unblinded, single-blinded or double blinded. Phase III trial participants are assigned to treatment groups by randomization. Building on the data from Phase I and II studies, Phase III trials aim to gather efficacy and safety data of a new treatment intervention in comparison with the current standard of care. These trials may also examine the clinical benefit of the intervention in different patient populations, using different dosages and in combination with other drugs.

While the endpoints of Phase III oncology trials are commonly overall survival (OS) or time to progression (TTP), progression-free survival (PFS) is often selected as a surrogate endpoint for OS in oncology trials as it reflects the true measure of first-line drug activity. However, controversy exists regarding the use of PFS as an endpoint. Even when supported by strong results from Phase II trials, failed Phase III oncology trials are quite common. In most of these cases, a statistically significant difference in PFS between treatment groups fails to translate into OS benefit. In the placebo-controlled Phase III AVADO and E2100 trials, which investigated the efficacy of bevacizumab added to chemotherapy as a first-line therapy for HER2-negative metastatic breast cancer, the addition of bevacizumab was shown to significantly increase PFS. However, in July 2010, the Oncology Drugs Advisory Committee (ODAC) voted that the breast cancer indication be removed from the bevacizumab label. One of the reasons for the removal was that while bevacizumab increased PFS in the Phase III trials, the magnitude of benefit did not translate into improved survival. The pros and cons of the use of PFS as a surrogate endpoint will be addressed in this session.

At the end of this presentation, participants should have an improved understanding of the essential elements of a Phase III trial. This will include defining the study objectives and primary endpoints, as well as the choice of study population.

KEY MESSAGES

- Phase III trials begin if evidence of effectiveness is shown in Phase II studies.
- The primary objective of Phase III clinical trials is to compare the effectiveness of a new treatment intervention with the current standard of care. If the new intervention is more effective than the usual treatment and/or is better-tolerated, it may become the new standard of care.
- The primary endpoints of Phase III oncology trials are often overall survival (OS) or time to progression (TTP). Progression-free survival (PFS) can be selected as a surrogate endpoint for OS.
- PFS remains a debatable surrogate endpoint in oncology trials.

Statistical issues in Phase III randomized clinical trials: interim analysis and data monitoring

Ning Li

In order to market a new drug, regulatory agencies are required to demonstrate the experimental drug’s efficacy and safety by conducting adequate and well controlled confirmative studies (Phase III). There are several key statistical issues in the design, analysis and conducting of Phase III studies. Among them, Interim Analysis (IA) and Adaptive Design and Data Monitoring have been the most frequently debated in recent years, especially since the US FDA published its draft guidance for these topics.

After this session, the audience should be able to understand the definition of interim analysis, the pros and cons of planning and performing an interim analysis, and its impact on the validity and integrity of a study. In addition, the audience should be able to understand the rationale behind the requirement of having an adaptive design and regulatory agencies’ concerns on such a design.

KEY MESSAGES

- An interim analysis may provide additional information regarding costs in the study.
- An adaptive design may provide an efficient way to demonstrate efficacy and safety; however, validity and integrity are major concerns.
- All trials need a data and safety monitoring plan.
- Some may need (or mandate) an IDMC.
- Plan ahead with a written charter and Standard Operating Procedure (SOP) if interim analysis or adaptive design is employed.
- No single statistical rule to be used for decision-making.
- Implications of an IDMC:
  - independence, confidentiality
  - trial safety, efficacy
  - trial quality, integrity; credibility.

Lessons learned from Avastin® clinical trials in breast cancer
Sandra M Swain, M.D.

Everyone involved in the controversy surrounding the utility of bevacizumab desires an improved outcome for patients with metastatic breast cancer (MBC) with a better quality of life. The U.S. Food and Drug Administration’s (FDA) accelerated approval mechanism was designed to make drugs more rapidly available to cancer patients, however, this cannot be done without a clear clinical benefit and identification of a specific patient population which truly benefits.

If the U.S. FDA decides to follow the Oncologic Drugs Advisory Committee (ODAC) recommendations, the use of bevacizumab would be considered “off-label”. Organizations such as the National Comprehensive Cancer Network (NCCN) and European Medicines Agency (EMA) have already reiterated their decision to keep the indication for bevacizumab in MBC independently of the U.S. FDA decision. However, if the U.S. FDA revokes bevacizumab approval for MBC, insurance companies may decide not to cover the costs of bevacizumab, and the majority of patients will not be able to afford the approximately US$90,000 annual cost of the drug. Regardless, Medicare has announced that bevacizumab would continue to be covered.

It is well accepted and recognized that bevacizumab is an active therapeutic agent in breast cancer. Three large-scale clinical trials (E2100, AVADO and RIBBON-1) documented highly reproducible results in terms of tumor response rates and progression-free survival (PFS) benefit. However, there are currently no validated biomarkers that allow for the definition of patient populations that will most likely respond to this therapy.

Unfortunately, the cost of cancer treatment is rising faster than the efficacy of cancer treatment. Even if the FDA and its advisors are not permitted to consider cost in their decisions, the oncology community is forced to face this reality. In a time of economic constraints, given the decrease in the quality of life with no survival benefit in E2100, the results available from AVADO and RIBBON-1, and the enormous cost of bevacizumab, it is difficult to justify the use of bevacizumab as first line therapy in all patients with MBC.

Lessons learned from gefitinib and crizotinib clinical trials in NSCLC

Shun Lu

In this presentation I will review the history of Gefitinib and Crizotinib. With the advent of new targeted agents it is becoming increasingly clear that a mechanistic understanding of each agent is very important. We are learning more and more about how target agents affect cell signalling pathway. Thus, an understanding of these molecular events is critical in clinical trial design. The use of prospective tumor genotyping has the potential to streamline cancer-treatment development.

本人在这项报告中回顾了Gefitinib与Crizotinib的发展史。随着靶向药物的出现，人们越来越重视了解每一个药物的作用机理，我们越来越了解靶向药物影响到了细胞信号传导通路，了解这些情况对于临床研究的设计是很重要的。前瞻性的利用基因分型可以提高抗肿瘤治疗的有效性

KEY MESSAGES

• It is time to change the paradigm, and begin thinking about directing therapy at a molecular target rather than developing organ-specific treatments.

• 我们应当改变现有的治疗模式，应该专注于特异性靶点的治疗，而不是仅仅关注器官特异性治疗

• To identify the history of Gefitinib and Crizotinib

• 回顾Gefitinib与Crizotinib的发展史

• To understand the scope and importance of gene analysis in NSCLC treatment

• 了解治疗NSCLC时基因分析的范围以及重要性
