Chugai Academy for Advanced Oncology

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International Academy for Advanced Oncology [IAAO]

IAAO

Kick-off Forum

2nd Announcement & Abstract

Theme

Current status and future view of predictive factors and new target molecules

Date: 1st day: 17:00~19:15, Friday, March 26th, 2010
2nd day: 9:00~16:30, Saturday, March 27th, 2010

Venue: [Pegasus] 1F, Hotel Nikko Tokyo
1-9-1 Daiba, Minato-ku, Tokyo 135-8625, Japan TEL: +81-3-5500-5500 FAX: +81-3-5500-2525

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Chugai Academy for Advanced Oncology
[CHAAO]

International Academy for Advanced Oncology

IAAO Kick-off Forum Organizer

Makoto Ogawa, MD
Emeritus President, Aichi Cancer Center, Japan (Governor of CHAAO)

Mitsuaki Yoshida, PhD
Director, Cancer Chemotherapy Center, JFCR, Japan (Governor of CHAAO)

Bruce Chabner, MD
Clinical Director of Cancer Center, Professor, Chief of Division of Hematology/Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, USA

Kiyohiko Hatake, MD, PhD
Director of Division of Medical Oncology, Hematology, Ambulatory Therapy Center, Newer Drug Development Center, Division of Clinical Chemotherapy, Cancer Chemotherapy Center, Olympus Bio-imaging Laboratory, Cancer Institute Hospital, Japan

Nobuyuki Mizunuma, MD
Director of Digestive Organ, Division of Medical Oncology, Cancer Institute Hospital, Japan

Contents

Greeting

– Introduction of the objectives and the future view of CHAAO/IAAO –

I am delighted to inform you that October 1, 2009, Chugai Pharmaceutical Co., Ltd. (hereafter, "Chugai") established the Chugai Academy for Advanced Oncology (CHAAO) aiming at contributing to the development of cancer treatment in Japan. The primary objective of this general incorporated association is to promote an even deeper academic exchange between the world's top-level specialists in the field of cancer and healthcare professionals who are playing a leading role in cutting-edge research and treatment of cancer in Japan.

Medically advanced nations of the world, especially in Europe and the United States, are ahead of Japan in carrying out a variety of innovative cancer-related programs aimed at making the benefits of cancer treatment equally available. Among their initiatives include raising patients' awareness of cancer treatment, promoting collaboration among patient groups, and spreading multidisciplinary care and standardized treatment.

Now that Chugai has become the top pharmaceutical manufacturer in the field of oncology, we feel that, as a corporation contributing to enhancing cancer treatment in Japan, we have the responsibility to take the initiative in conducting assistance activities to raise our country's cancer treatment to worldwide levels as soon as possible.

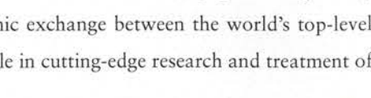
We feel that as a general incorporated association, this Academy can contribute to the development of the cancer treatment infrastructure in Japan as well as to the future advancement of cancer treatment from a standpoint different from usual corporate activities. We are convinced that activities such as these will ultimately lead to the realization of cancer treatment which allows patients to confront cancer proactively and with hope.

Objectives of activities

- Draw innovative roadmaps of cancer research and treatment in Japan, and build a worldwide cancer treatment network.
- Promote the spread of trans-relational research that includes molecular-target treatments and their biomarkers, as well as clinical research and standard treatment in order to realize innovative drug discoveries and world-standard cancer treatment.
- Grasp the current status and problems of Japan's healthcare system, set up reform goals with an eye to the future, and make proposals.

Primary activities

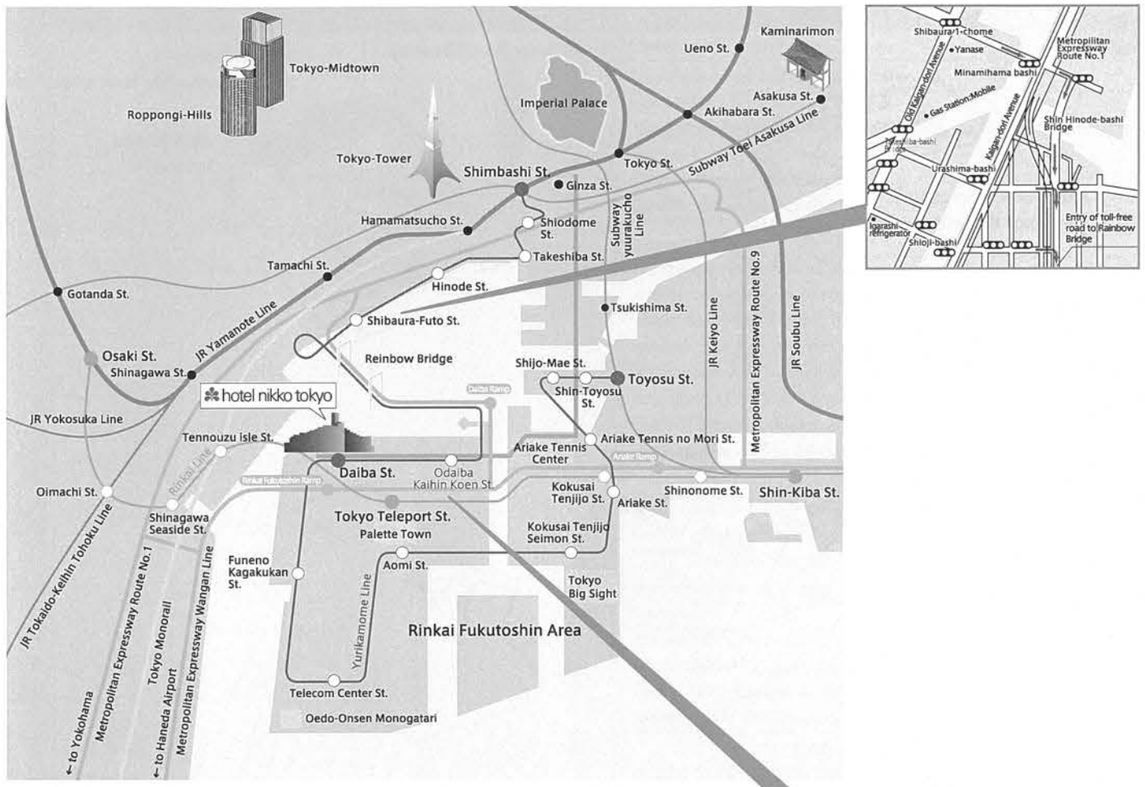
- Holding of oncology forums including consensus meetings
- Cancer research aid programs, etc.



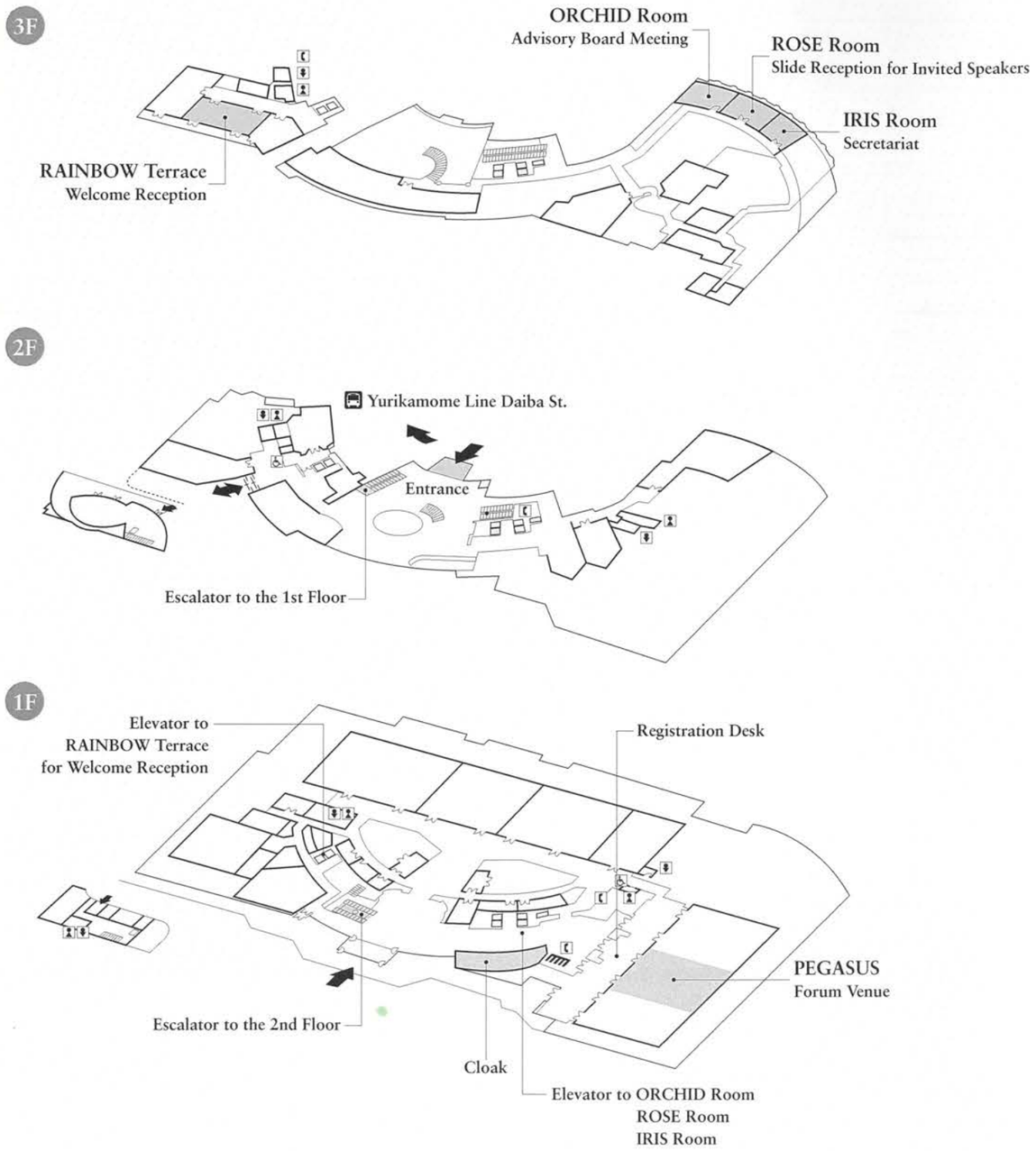
Osamu Nagayama

Representative Governor, 'Chugai Academy for Advanced Oncology' (CHAAO), Incorporated Association

Access to the Venue



Floor Plan



Program at a Glance

Date	March 26th 2010 Friday	Date	March 27th 2010 Saturday
Place	[Pegasus] 1F	Place	[Pegasus] 1F
		8:30	**Opening of the 2nd Day**
		8:50	**Introduction of 2nd day by secretary**
		9:00	**Symposium-1:** by Invited Speaker Search and establishment of biomarkers for cancer as predictive factors-1 **Chair: Mitsuaki Yoshida, PhD** **Speaker: Klaus Pantel, MD**
		10:00 10:15	Coffee Break (15 min)
		10:15	**Symposium-2:** by invited speaker Search and discovery of new cancer agents **Chair: Kiyohiko Hatake, MD** **Speaker: Lyndsay N. Harris, MD**
		11:15	**Symposium-3-1:** by invited speaker Prediction of response and tolerance of cancer drugs **Chair: Chikashi Ishioka, MD** **Speaker: Napoleone Ferrara, MD**
		12:15 13:05	Lunch Time (50 min)
		13:05	**Symposium-3-2:** by invited speaker Prediction of response and tolerance of cancer drugs **Chair: Masakazu Toi, MD** **Speaker: Hasan Korkaya, DVM, PhD**
		14:05	**Overview** Clinical developments of molecular biology for individualized cancer therapy **Chair: Yuko Kitagawa, MD** **Speaker: Eric Van Cutsem, MD, PhD**
		15:05 15:20	Coffee Break (15 min)
		15:20	**Review and Consensus Meeting by all participants:** Issues and future aspects of translational reseatch for clinical research and the practice Clinical developments of molecular biology for individualized cancer therapy **Chair: Kiyohiko Hatake, MD** **Co-Chair: Nobuyuki Mizunuma, MD** **Presenter: Kiyohiko Hatake, MD**
		16:20 16:30	**Closing Remarks & Acknowledgement** **Makoto Ogawa, MD**
16:00	**Registration of participation: [Pegasus] 1F, Main Bldg.**		
	16:00-16:30 Slide reception for speakers: **Place: [Rose Room] 3F** 16:30-16:55 Preliminary Meeting with inviting speakers and chairs **Place: [Rose Room] 3F**		
	16:00-16:30 **IAAO Advisory Board Meeting** **Place: [Orchid Room] 3F**		Closing of IAAO Kick -off Forum
17:00 17:15	**Opening Address** **Mr. Osamu Nagayama**		
17:15	**Plenary Session-1:** by Invited Speaker Present status and future view of molecular targeting therapy for cancer- Viewpoint of individualized cancer therapy- **Chair: Makoto Ogawa, MD** **Speaker: Bruce A. Chabner, MD**	17:00 18:00	**IAAO Advisory Board Meeting:** **Place: [Orchid Room] 3F**
18:15	**Plenary Session-2:** by Invited Speaker The Practicalities and Future of individualised intervention for cancer patients **Chair: Chikashi Ishioka, MD** **Speaker: Patrick G. Johnston, MD**		
19:15	Move to the reception room, : [Rainbow Terrace] 3rd floor		
19:30 21:00	**Welcome Reception** Opening Address: Masaki Kitajima, MD, Honorary FRCS, FACS **Place: [Rainbow Terrace] 3F, Annex Bldg.**		

Plenary Lecture 1:

Speaker: **Bruce A. Chabner, MD**
Clinical Director of Cancer Center, Professor and Chief of Division of Hematology/Oncology,
Massachusetts General Hospital, Harvard Medical School, Boston, USA

Chair: **Makoto Ogawa, MD**
Emeritus President, Aichi Cancer Center, Japan

[Speaker's Biographical Sketch]

Professor Bruce A. Chabner, M.D.
Professor, Department of Medicine, Harvard Medical School Clinical Director, MGH Cancer Center, Massachusetts General Hospital

Contact Information

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Specialties & Programs

Hematology/Oncology
Department of Medicine

Clinical Interests

Breast Cancer
New Cancer Drugs
Non-Hodgkin's Lymphoma

Medical Education

MD, Harvard Medical School
Residency, Brigham & Women's Hospital

Board Certifications

Medical Oncology, American Board of Internal Medicine
Internal Medicine, American Board of Internal Medicine

Research Abstract

Major interest is in the clinical testing, pharmaco-kinetics, and biochemical pharmacology of new anticancer drugs, particularly natural products and signal transduction inhibitors.

Introduction

Dr. Bruce Chabner is the Clinical Director of Massachusetts General Hospital Cancer Center, the Chief of Hematology/Oncology at MGH and Professor of Medicine at Harvard Medical School.

His main fields of research focus on the biochemistry and pharmacology of folate antagonists, experimental therapeutics, and clinical trial design.

He served as the Associate Director of Clinical Science at Dana Farber/Harvard
Cancer Center and has held additional academic appointments, including the position of Director of the Division of Cancer Treatment of the National Cancer Institute from 1982 to 1995.

Dr. Chabner received his B.A. from Yale College (1961) and M.D. from Harvard Medical School (1965).

He has authored and edited the standard text, Principles and Practice of Cancer Chemotherapy and Biological Response Modifiers, now in its fourth edition. Dr. Chabner has contributed to the Goodman and Gilman textbook of Pharmacology and has authored chapters for numerous other textbooks of internal medicine, hematology, oncology and pharmacology.

Over the years, Dr. Chabner has received awards including Phi Beta Kappa, Alpha Omega Alpha, the Public Health Service's Distinguished Service Medal, the Karnofsky Award of the American Society for Clinical Oncology and the Bruce F. Cain Award for Drug Development of the American Association for Cancer Research. In addition, Dr. Chabner was awarded the Bob Pinedo Prize in 2006 (The Bob Pinedo Cancer Care Prize Recipient 2006).

Also, Dr. Chabner is Editor-in-Chief of the Oncologist and serves on the executive advisory boards for some of the industry's leading innovators in drug development.

Dr. Chabner is an internationally recognized top leader of cancer drug discovery and development.
Also, we are honored so much that Dr. Chabner accepted an Advisory Board Member of IAAO as USA representative.

Plenary Lecture 1:

-Present status and future view of molecular targeting therapy for cancer -Viewpoint of individualized cancer therapy-

Phase I Trials at a Crossroads: Proof of Antitumor Activity as Primary Objective

Bruce A. Chabner, MD
Director of Clinical Research
Massachusetts General Hospital Cancer Center, USA

In former times, Phase I trials in oncology sought to establish a safe dose and schedule for new compounds. Pharmacokinetic studies established a rational basis for changing schedule and understanding the relationship of dose to exposure (Area under the curve: AUC). The patients for such trials were selected primarily on the basis of performance status and normal organ function, i.e. good "physiological" subjects for the study of a new drug. Their tumors were secondary considerations. Clinical responses were rare (less than 5% of patients), but did provide clues for further directions in drug development. With the rapid expansion of targeted drug discovery and development, the paradigm for Phase I trials has shifted significantly. These trials are now regarded as an early opportunity to validate the concept that inhibition of the target will slow tumor growth or lead to tumor regression. While the basic elements of the trial (dose escalation in a "physiologically intact" population, coupled with PK studies) has not changed, the assessment of clinical response in a highly selected patient population, enriched for tumors that carry the target of interest, has become a primary goal. If the tumor contains the target, and the drug levels are achievable, then the tumor should respond to treatment.

In this lecture, I will illustrate the strength of this new approach by comparing the development of two targeted compounds: inhibitors of the epidermal growth factor receptor (EGFR), and inhibitors of c-met/alk kinase. In the former instance, gefitinib and erlotinib were developed in broad-based, unselected patient populations, with a small number of responses, primarily in non-small cell lung cancer (NSCLC). Further development in Phase II and III trials established erlotinib as a modestly active drug in a general lung cancer population. Only in retrospect was it appreciated that a distinct subset of NSCLC patients with activating mutations in EGFR were highly responsive to both of these drugs. Six years after its initial approval, and then withdrawal for lack of activity, gefitinib was won a new life as a potent inhibitor of EGFR mutant non-small cell lung cancer.

By contrast, the recent clinical development of inhibitors of the ALK kinase has proceeded rapidly in a highly selected patient population. In a carefully planned Phase I trial, with expansion at the maximum tolerated dose to include 60 patients with EML4/ALK activating translocations, the Pfizer c-met/alk inhibitor proved to be highly active (65% response rate, 20% stable disease) in these selected patients. Without the need for a Phase II study, a Phase III randomized trial comparing the new drug against standard therapy will start shortly. Patients with other kinds of tumors that contain activating mutations in ALK, including neuroblastoma, and colon cancer will also be included in other Phase II trials.

The alk inhibitor study, as well as others recently reported with inhibitors of b-RAF and c-kit in melanoma, and a hedgehog pathway inhibitor in basal cell cancer, all support the strategy of selecting patients according to molecular profiling of tumors in early "proof of concept" trials. The results in Phase I can establish the clear value of new drugs in selected subsets of patients. The implications of this new strategy are significant:

(1) Molecular profiling of metastatic tumors will be essential to allow appropriate patient selection for early clinical trials, and, as the numbers of approved targeted drugs increases, ultimately for standard therapies.
(2) Early drug trials will require the co-operation of multiple cancer centers, particularly in their expansion phase, to find adequate numbers of appropriate patients, since many of the interesting mutations occur in small subsets of various tumors.
(3) New technology, such as molecular imaging and/or the isolation of circulating tumor cells in large numbers, will be required to establish that drug dose and schedule are optimal for inhibiting the target molecule.
(4) Early studies of mechanisms of drug resistance may inform the design of Phase II trials of drug combinations.

Plenary Lecture 2:

Speaker: **Patrick G. Johnston, MD**
Professor, Centre for Cancer Research & Cell Biology, Dean, School of Medicine and Density,
The Queen's University of Belfast, Belfast City Hospital, Belfast, Northern Ireland, UK

Chair: **Chikashi Ishioka, MD**
Professor, Department of Clinical Oncology, Tohoku University School of Medicine, Japan

[Speaker's Biographical Sketch]

Professor Patrick Johnston received his MB BCh degree in Medicine with distinction from University College Dublin in 1982. This was followed by an internship and senior house officer internal medicine training at the Mater and St James's University teaching hospitals, also in Dublin, until 1985. From 1985-1987 he pursued his initial training in Oncology and Haematology in the Mater Hospital, University College Dublin, during which time he attained his doctoral degree.

In 1987 he obtained a fellowship at the National Cancer Institute, NIH, USA where he began to pursue further clinical training in medical oncology and his post-doctoral studies in molecular pharmacology and drug development. During this time he defined the regulation and clinical relevance of the nucleotide synthetic enzyme thymidylate synthase (TS); a key cancer therapeutic target and completed a number of phase I clinical studies using antifolate therapies such as tomudex in patients. As a result of this work he was promoted to senior investigator status at the NCI in 1991. During this time, he also received the Young Investigator Award from the American Society of Clinical Oncology and the Technology Award from the National Cancer Institute.

In 1996 he was appointed Professor of Oncology at Queen's University Belfast and since then he has led the development of a comprehensive cancer centre for Northern Ireland encompassing a state-of-the-art Clinical Cancer Centre (£65 million) which opened in March 2006, and also a £25 million major cancer research complex - the Centre for Cancer Research and Cell Biology at Queen's - of which he was Director until August 2007. This interdisciplinary research centre has as its major emphasis translational research, and houses over 300 researchers from all over the world. Professor Johnston has also led the development of a number of international research collaborations, most notably the creation of the NCI–All Ireland Cancer Consortium which was signed in 1999 and renewed in 2006. This Consortium, which encompasses the Departments of Health in Ireland, North and South, and the Departments of Health and Human Services in the US (www.allirelandnci.org) has created training opportunities and collaborative research programmes for a large number of professionals involved in cancer care and cancer research throughout the island of Ireland.

He has continued his research work utilising genomic-based technologies to define the transcriptional changes induced in tumours by cytotoxic agents such as 5-FU and Oxaliplatin and identifying groups of genes whose expression may predict for response or toxicity to these therapies. Using this approach he has identified that the extrinsic apoptosis pathway regulated by death receptors and c-FLIP is important in mediating cell death to chemotherapy and are currently developing new strategies to target this pathway. In addition, he has recently developed disease-specific transcriptome arrays which have allowed access to molecular gene expression studies using formalin-fixed paraffin-embedded tissues. As a result, he has begun to use this unique technology to develop clinical classifiers of disease prognosis and chemotherapeutic response in colorectal cancer patients, in collaboration with US and European clinical co-operative groups. This development has led to the creation of Almac Diagnostics (www.almacdiagnosticscom), a biotech spin-out company delivering array-based genomic tools for prediction of therapeutic outcome in patients with cancer.

Professor Johnston has published over 200 peer review articles and co-edited 5 textbooks, including 'Oncologic Emergencies'. He sits on a number of national and international scientific boards, including the MRC, American Society of Clinical Oncology and the Singapore Cancer Syndicate Board, and is on the editorial boards of several leading international oncology journals, including The Oncologist, Journal of the National Cancer Institute, Clinical Cancer Research, Clinical Colorectal Cancer and PLoS Medicine.

He was appointed as Dean of the School of Medicine, Dentistry and Biomedical Sciences and Director of the Institute of Health Sciences at Queen's University Belfast in September 2007.

Plenary Lecture 2:

THE PRACTICALITIES AND FUTURE OF INDIVIDUAL INTERVENTION FOR CANCER PATIENTS

Patrick G Johnston, MD
Dean, School of Medicine, Dentistry and Biomedical Sciences and Professor of Oncology,
Centre for Cancer Research and Cell Biology, Queen's University Belfast, UK

Abstract

Genomic technologies have enabled the evaluation of genomic alterations on a genome-wide scale and significantly altered genomic marker research in solid tumours. The traditional model of identifying a particular genomic alteration and evaluating the association between this and a clinical outcome measure is no longer feasible within clinical studies. This has created challenges in considering the use of genomic markers in cancer care such as clinical study design, reproducibility and interpretation and reporting of results. My talk will explore these challenges, focusing on high-throughput genomic technology and using colorectal cancer as a primary example. I will highlight some common failings in study design that have impacted on the clinical usefulness of putative genomic markers.

A shift in clinical trial design allows genomic markers to be incorporated into prospective studies as patient stratification tools. In so doing, genomic markers can be evaluated in a rigorous fashion, facilitating the implementation of such markers into routine clinical practice and enabling the rational and tailored use of cancer therapies for individual patients.

Learning points:

- Despite extensive research, relatively few genomic markers have been implemented into routine clinical use to date, often due to failings in clinical study design.
- The traditional 'single disease, single genomic marker' approach fails to take account of tumour heterogeneity and consequently single genomic markers are often found to be inadequate biomarkers in clinical studies.
- The introduction of new high-throughput genomic technologies has enabled the simultaneous measurement of multiple genomic alterations, revolutionising the field of genomic marker research in oncology.
- These technologies in turn have presented new challenges to considering the routine clinical use of putative genomic markers such as reproducibility and interpretation and reporting of results.
- Novel genomic markers should undergo extensive validation prior to considering their implementation into routine clinical practice.
- A shift in clinical trial design, incorporating genomic markers into prospective studies as a patient stratification tool, and evaluating such markers in a rigorous, focused and timely fashion would facilitate their implementation into clinical use.

Symposium 1:

Speaker: **Klaus Pantel, MD**

Professor and Director, Institute of Tumor Biology, Center of Experimental Medicine, University Medical Center, Hamburg, Germany

Chair: **Mitsuaki Yoshida, PhD**

Director, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Emeritus Professor, University of Tokyo, Japan

[Speaker's CV]

ADDRESS

Klaus Pantel, M.D., Ph.D.,

Professor of Molecular Genetics Institute of Tumor Biology University Hospital Hamburg-Eppendorf Martinistreet 52 D-20246 Hamburg, Germany
Tel.:+ 49-40-74 10-53503 FAX:+ 49-40-74 10-55379

PERSONAL DATA

Born: August 3, 1960 Bergisch Gladbach, Germany

EDUCATION

1980-1986	University of Cologne, School of Medicine, Germany. Medical Training, Degree: M.D.
1983-1987	University of Cologne, Medical Clinic I, Germany. Thesis: Mathematical Modeling in Hematopoiesis, Degree: Ph.D. (Advisor: Dr. H.E. Wichmann)
1987-1989	Postdoctoral DG-Fellow, Division of Hematology and Oncology, Department of Internal Medicine, Wayne State University School of Medicine, Detroit, MI, USA. (Advisor: Dr. A. Nakeff), Subject: Influence of T-lymphocytes and NK-cells on the regulation of haematopoesis
1989-1995	Habilitation in "Immunology" at the Medical Department of the Ludwig-Maximilians-Universität Munich, Institute of Immunologie, Degree: Dr. med. habil. ("Associate Professor"), Subject: Immunocytochemical and molecular analyses on the diagnosis, clinical relevance and pathophysiology of minimal residual disease in cancer patients

PROFESSIONAL APPOINTMENTS

1999-2001	Full Professor (C3) in Molecular Genetics, Department of Gynecology and Obstetrics, University Hospital Eppendorf, University of Hamburg, Germany Head of Molecular Oncology, Department of Gynecology and Obstetrics, University Hospital Eppendorf, University of Hamburg, Germany
2002-present	Director of the new Institute of Tumor Biology, Full Professor (C4) in Tumor Biology, University Hospital Eppendorf (UKE), University of Hamburg, Germany
2002-2008	Deputy Director of the new Center of Experimental Medicine, UKE
2002-present	Coordinator of the Oncology Research Program at UKE

Organisation of International Scientific Meetings

2005	5th International Symposium on Minimal Residual Cancer, San Francisco, USA
2006	2006 Workshop on Tumor Cell Dormancy, NIH, Bethesda, USA
2007	6th International Symposium on Minimal Residual Cancer, Hamburg, Germany

Editorial Boards

since 1998	Co-editor for area Immunology of the Journal "Tumour Diagnostic & Therapy"
since 1999	Associate Editor of the Journal "Cytotherapy"
	Associate Editor of the Journal "Clinical Cancer Research"
since 2001	Member of the Editorial Board of "Cancer Research and Clinical Oncology"
since 2003	Member of the Editorial Board of "Journal of Translational Research"
since 2004	Member of the Editorial Board of "Current Cancer Therapy Reviews"
since 2005	Associate Editor of "Breast Cancer Research"
since 2007	Member of the Independent Review Committee (IRC) for the TRANSBIG Network
since 2008	Member of the Editorial Board of the "Journal of Epithelial Biology & Pharmacology"

Membership in Scientific Societies

1989	International Society for Experimental Hematology
	American Society of Hematology
1990	German Society for Immunology
	German Society for Cell Biology
	German Society for Hematology and Oncology
1991	American Association for Cancer Research
1991	German Cancer Society
1993	International Society for Cell Therapy
1993	International Society for Hematotherapy & Graft Engineering
2007	Metastasis Research Society

Reviewer Activities

•German Research Foundation ("Deutsche Forschungsgemeinschaft") •American Journal of Pathology •Annals of Hematology •British Journal of Cancer •Cancer Research •Clinical and Experimental Immunology •Clinical Cancer Research •European Journal of Cancer •EORTC Translational Research Advisory Committee •Immunobiology •Journal of Hematotherapy •Journal of Molecular Medicine •Journal of the National Cancer Institute •Molecular Medicine Today •Nature Medicine •The Lancet

Publication List

A.Contributions in peer-reviewed journals

1. Alix-Panabieres C, Vendrell JP, Slijper M, Pelle O, Barbotte E, Mercier G, Jacot W, Fabbro M, Pantel K. Full length cytokeratin-19 is released by human tumor cells: a potential role in metastatic progression of breast cancer. Breast Cancer Res 2009;11: R39.
2. Koenig AM, Prenzel KL, Bogoevski D, Yekebas EF, Bubenheim M, Faithova L, Vashist YK, Gawad KA, Baldus SE, Pantel K, Schneider PM, Holscher AH, Izbicki JR. Strong impact of micrometastatic tumor cell load in patients with esophageal carcinoma. Ann Surg Oncol 2009;16: 454-62.
3. Muller V, Pantel K. HER2 as marker for the detection of circulating tumor cells. Breast Cancer Res Treat 2009;117: 535-7.
4. Pantel K, Riethdorf S. Pathology: are circulating tumor cells predictive of overall survival? Nature Rev Clin Oncol 2009;6: 190-1.
5. Riethdorf S, Pantel K. Clinical relevance and current challenges of research on disseminating tumor cells in cancer patients. Breast Cancer Res 2009;11 Suppl 3: S10.
6. Schwarzenbach H, Alix-Panabieres C, Muller I, Letang N, Vendrell JP, Rebillard X, Pantel K. Cell-free tumor DNA in blood plasma as a marker for circulating tumor cells in prostate cancer. Clin Cancer Res 2009;15: 1032-8.
7. Slade MJ, Payne R, Riethdorf S, Ward B, Zaidi SA, Stebbing J, Palmieri C, Sinnett HD, Kulinskaya E, Pitfield T, McCormack RT, Pantel K, Coombes RC. Comparison of bone marrow, disseminated tumour cells and blood-circulating tumour cells in breast cancer patients after primary treatment. Br J Cancer 2009;100: 160-6.
8. Wrage M, Ruosaari S, Eijk PP, Kaifi JT, Hollmen J, Yekebas EF, Izbicki JR, Brakenhoff RH, Streichert T, Riethdorf S, Glatzel M, Ylstra B, Pantel K, Wikman H. Genomic profiles associated with early micrometastasis in lung cancer: relevance of 4q deletion. Clin Cancer Res 2009;15: 1566-74.
9. Kalinina T, Bockhorn M, Kaifi JT, Thieltges S, Gungor C, Effenberger KE, Strelow A, Reichelt U, Sauter G, Pantel K, Izbicki JR, Yekebas EF. Insulin-like growth factor-1 receptor as a novel prognostic marker and its implication as a Co-Target in the treatment of human adenocarcinoma of the esophagus. Int J Cancer.
10. Grabinski N, Grupp K, Pantel K, Brandt B, JückerM.AKT3 knockdown suppresses proliferation, survival and migration of disseminated tumor cells from a patient with non-small cell lung cancer (NSCLC) J Cancer Res, submitted.

B.Contributions for Books

2008

1. Müller V, Alix-Panabières C, Pantel K: Detection of minimal residual disease in predicting outcome, chapter 7, in Prognostic and Predictive Factors in Breast Cancer, Walker, 2008, pp 88-96.
2. Alix-Panabières C, Pantel K: Chapter Micrometastasis in Encyclopedia of Cancer, Springer Verlag, in press.
3. Alix-Panabières C, Rugo HS, Park JW, Pantel K: Circulating and Disseminated Tumor Cells from Solid Tumors: Research and Clinical Perspectives, Chapter 21, in From Local Invasion to Metastatic Cancer: Involvement of Distant Sites through the Lymphovascular System, Springer, in press.
4. Pantel K, Wikman H, Alix-Panabieres C, Effenberger K, and Riethdorf S. Critical issues of research on circulating and disseminated tumor cells in cancer patients. Chapter in Cancer Metastasis: Biologic Basis and Therapeutics, Cambridge University Press, Editors Drs. Welch, Lyden, and Psaila, in press.

2009

5. Riethdorf S, Pantel K. Disseminierte Tumorzellen im Knochenmark – Detektionsmethoden, Charakterisierung und klinische Relevanz. Zeller, zur Hausen. Onkologie. 26. Erg. Lfg. 9/09. Allgemeine Tumordiagnostik, 2009; 1-38.
6. Riethdorf S, Müller V, Panabieres C, Pantel K. Detection and Characterization of Disseminated Tumor Cells present in Bone Marrow of Cancer Patients. Bone and Cancer, Topics in Bone Biology 5, Springer 2009; 103-17

Symposium 1:

-Search and establishment of biomarkers for cancer as predictive Factors-

Molecular and functional characterization of circulating tumor cells as diagnostic and therapeutic targets

Klaus Pantel, MD

Institute of Tumor Biology, Center of Experimental Medicine,
University Medical Center Hamburg-Eppendorf, Germany

Metastatic relapse of carcinoma patients is mainly due to clinically occult micrometastases present at primary diagnosis, but undetectable even by high-resolution imaging technologies. Frequently, traditional prognostic factors are insufficient to predict metastasis and treatment decisions are mainly based on statistical risk parameters. Highly sensitive and specific cytometric and molecular methods enable now the detection of disseminated tumor cells (DTC) in bone marrow (BM) and circulating tumor cells (CTC) in peripheral blood of breast carcinoma patients. The presence of DTC has independent prognostic impact for patients with primary breast cancer with regard to metastatic relapse and overall survival (1) and DTC may even contribute to local relapse (2).

Interestingly, bone marrow seems to be a common homing organ for cells derived from various epithelial tumors including breast, prostate, lung and colon cancer (3); (4). This surprising finding is consistent with recent results obtained in mouse models (5),, supporting the hypothesis that BM might be an important reservoir for metastatic cells from where they can re-circulate into various organs and may be even back to the primary site (6); (7); (8). DTC may have adapted to the special environmental conditions in the BM and may survive in so called "bone marrow niches" over decades. This hypothesis has important clinical implications for the design of future clinical trials with drugs that are able to specifically block the interaction between tumor cells and the bone marrow microenvironement (e.g. bisphosphonate or antibodies to RANK ligand).

However, a significant fraction of DTC remain over years in a "dormant" stage, and little is known about the conditions required for the persistence of dormancy or the escape from the dormant phase into the active phase of metastasis formation (9). Transition from a dormant into a dynamic phase may be caused by genetic changes within the disseminated tumor cells (i.e. acquisition of growth factor receptor Her-2/neu amplification (10); (11) but also by the influence of the surrounding bone marrow microenvironment.

Furthermore, BM has a particular capability to host stem cells, which may also contribute to keep DTC in a stem cell-like state. This assumption is also supported by the fact that most DTC in BM and blood are in a non-proliferating state and survive systemic chemotherapy (12); (13)). Moreover, most DTC in breast cancer patients showed a breast stem cell phenotype (CD44+/CD24- or MUC1-/CK19+) (14); (15)). Moreover, epidermal growth factor (EGF) and fibroblast growth factor-2 (FGF-2) – two known stem cell factors – were relevant for the in vitro growth of DTC obtained from BM of cancer patients (Solakoglu et al., PNAS 2002). Nevertheless, strong direct evidence that some of the few DTC or CTC detected in the BM or blood samples have cancer stem cell properties is still missing. Future studies including xenotransplantation of DTC/CTC into immunodeficient mice need to demonstrate that these cells are the actual founder cells of overt metastasis.

BM analyses are not well accepted by the medical community for the clinical management patients in breast cancer and other solid tumors. Therefore, most current research efforts are directed to evaluate the clinical utility of CTC detection (16). Because of the high variability of results obtained by different cytometric and molecular approaches, standardization of current technologies is urgently required (17); (18). While the prognostic significance of CTC could be demonstrated for metastatic breast cancer patients (Hayes & Smerage, CCR 2008), studies on the impact of CTC in primary breast cancer patients are still ongoing but the intermediate results are so far promising (9). Moreover, encouraging results on monitoring CTC during primary systemic or adjuvant chemotherapy in breast cancer patients were obtained in recent studies.

Further characterization of CTC is pivotal to understand the biology of tumor cell dissemination (19). The molecular characterization of CTC with special emphasis on potential cancer stem cell features and therapeutically relevant targets such as HER2 (19) might improve individual risk assessment and stratification of patients for targeted therapies. The HER2 proto-oncogene is currently the most predominant biological target for systemic therapy with remarkable results of clinical trials using a humanized monoclonal antibody (trastuzumab) in breast cancer. The detection of HER2-positive DTC/CTC might enable a "real-time" assessment of the HER2 status during the clinical course of disease. Several groups reported a striking discrepancy between the detection of HER2-positive DTC/CTC and the HER2 score of the corresponding primary tumor, suggesting that a small subclone of HER2-overexpressing cancer cells easily missed by routine primary tumor analysis may have the potential to disseminate (9). The detection of Her2-positive DTC and CTC was correlated to an unfavourable clinical outcome in breast and oesophageal cancer and HER2 gene amplification can be acquired during tumor progression of the cancer (10); (19); (20). Thus, the assessment of the HER2 status on DTC and CTC might add important information for the clinical management of cancer patients.

The characterization of DTC/CTC will contribute to more "tailored" and personalized anti-metastatic therapies. At present, the success or failure of anti-cancer therapies is only assessed retrospectively by the absence or presence of overt metastases during the post-operative follow up period. Real-time monitoring of peripheral blood (i.e., during and after systemic adjuvant therapy) for CTC might provide unique information for the clinical management of the individual cancer patient and allow an early change in therapy years before the appearance of overt metastases signals incurability (20). Future clinical trials will show whether the assessment and monitoring of therapeutic targets (e.g., EGF-R, HER2 or VEGF) on CTC (and probably DTC) might become an important diagnostic tool for cancer patients undergoing targeted therapies and may provide new insights into the selection of tumour cells under biological therapies.

Symposium 2:

Speaker: **Lyndsay N. Harris, MD**
Associate Professor and Co-Director, Breast Cancer Program, Yale Medical Oncology, New Haven, USA

Chair: **Kiyohiko Hatake, MD, PhD**
Director of Division of Medical Oncology, Hematology, Ambulatory therapy center, Newer drug development center, Division of Clinical Chemotherapy, Cancer Chemotherapy Center, Olympus Bio-imaging Laboratory, Cancer Institute Hospital, Japan

[Speaker's CV]

School
Yale University School of Medicine (and Yale University School of Nursing)

Education
B.Sc. University of Alberta, Edmonton, Canada, 1984
M.D. University of Alberta, 1988

Career/Academic Appointments
1994-1996 Instructor in Medicine, Georgetown University Medical Center, Washington, DC
1996-1999 Assistant Professor of Medicine, Duke University Medical Center, Durham, NC
1999-2005 Assistant Professor, Harvard Medical School
2006- Associate Professor of Medicine, Yale University School of Medicine, New Haven, CT
2006- Director, Breast Cancer Disease Program, Yale University School of Medicine, New Haven, CT
2007- Associate Clinical Professor, Yale University School of Nursing, New Haven, CT

Administrative Positions
2005-present Director, Breast Cancer Disease Program, Yale Univ. School of Medicine, New Haven, CT

Board Certification
•Royal College of Physicians and Surgeons of Canada, Internal Medicine Certificate, 1992 •Royal College of Physicians and Surgeons of Canada, Medical Oncology Certificate, 1993 •American Board of Internal Medicine Certificate, 1994 •American Board of Internal Medicine, Medical Oncology Certificate, 1995

Lectures, Courses, Web-based Education
2008 ASCO/ACS Breast Cancer Symposium Invited Faculty Tumor Board Controversy Session "Locally Advanced Breast Cancer. Invited Speaker "IGFIR Targeted Therapies"
2008 DOD Breast Cancer Symposium Invited Moderator "Controversies in HER2 positive Breast Cancer" and "Targeted Therapies, are we Hitting the Mark?"
2008 ASCO Invited Faculty, Chicago
2008 ASBS Satellite Symposium, "Pre-operative systemic therapy for HER2+ breast cancer: What has been learned?", NYC
2008 Lawrence & Memorial Clinical Science Lecture, New London, CT
2008 Current Trends in Breast Cancer, "Evolving Insights into Molecular Subtypes," NYC
2007 San Antonio Breast Cancer Symposium, "The HER2 amplicon gene FLJ20940 (PP1R1B) is upregulated in trastuzumab sensitive human breast cancer cell lines and HER2 amplified tumors that achieve a complete response to preoperative therapy" and "Role of host immune response genes in the clinical response to trastuzumab-based therapies," San Antonio, TX

PROFESSIONAL SERVICE

National/International Committees
2009-present Study chair, Pan American Cancer Trials (PACT) Network Data and Safety Monitoring Board (DSMB)
2009-present Duke DSMB Breast Study Group
2009-present Chair, Novartis DSMB (breast cancer adjudication panel)

Journal Service
Reviewer:
•Journal of Clinical Oncology •Clinical Cancer Research •New England Journal of Medicine •Cancer Research •Cancer •Breast Cancer Research and Treatment •Journal of the National Cancer Institute

Professional Organizations
•American Society of Clinical Oncology (ASCO) •American Association for Cancer Research (AACR) •Cancer and Leukemia Group B (CALGB)

University Committees
2006- Protocol Review Committee

Hospital Boards & Committees
2006- Breast Cancer Tumor Board

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6.Abu-Khalaf MM, **Harris L**. Anthracycline-induced cardiotoxicity: risk assessment and management. Oncology (Williston Park). 2009 Mar;23(3):239, 244-252. No abstract available.
7.Agarwal S, Zerillo C, Kolmakova J, Christensen JG, **Harris LN**, Rimm DL, DiGiovanna MP, Stern DF. Association of constitutively activated hepatocyte growth factor receptor (Met) with resistance to a dual EGFR/Her2 inhibitor in non-small cell lung cancer cells. Br J Cancer. 2009 Mar 24;100(6):941-9.

Reviews, Chapters, Books (list from earliest to most recent):
Abu-Khalaf, MM, **Harris LN**, Chung GG. DNA and Tissue Microarrays. In : Shergill, Iqbal S, Ayra, Manit and Patel, Hiten eds, *Basic Science Techniques in Clinical Practice*, Springer-Verlang London Ltd, UK. 2007, 98-108
Kang, SP; Martel, MB; **Harris, LN**. Triple negative breast cancer: current understanding of biology and treatment options. *Curr Opin Obstet Gynecol* 2008 Feb;20(1):40-6. *Review*
Abu-Khalaf M, **Harris LN**. Anthracycline-Induced cardiotoxicity: risk assessment and management. *Oncology* 2009, 239-252
Mayer T, **Harris LN**, DiGiovanna MP. Drugs targeting insulin-like growth factor 1 receptor. *Breast Cancer Online* 2009, 12(4), 1-10
4.Guidelines and Consensus Statements
A. National
American Society of Clinical Oncology Tumor Marker Guidelines, 2007

Symposium 2:

-Search and discovery of new cancer agents-

Abstract: Search and Discovery of New Cancer Agents for Breast Cancer

Lyndsay N. Harris, MD
Breast Cancer Program, Yale Medical Oncology, New Haven, USA

As we attempt to improve treatment of breast cancer it is critical that we better define breast cancer subtypes to optimize the use of standard and targeted therapies. Newer technologies have led to the recognition of different breast tumor subtypes and these discoveries have improved our ability to define optimal treatments for patients based on a better understanding of the biology of these subtypes. This overview will discuss the basic molecular definition of breast tumor subtypes and how this information is applied to the optimization of treatment for breast cancer patients.

The seminal work by Perou and Botstein, using microarray profiling to define the 'intrinsic subtypes', was the first publication to describe a molecular classification of breast cancer. Among the categories emerging from this study are the two categories of ER and/or PR positive (Luminal A and B) tumors, HER2 gene amplified (HER2-enriched) tumors and ER/PR negative, HER2 negative (Basal-like) tumors. Despite differences in the platforms used for gene expression analysis, these subtypes can be identified using microarray patterns from independent datasets. [1-4] While other categories of breast cancer exist (and will be added to the taxonomy) this classification reflects major subgroups of ductal breast cancer that are now used to subdivide patients when making treatment decisions.

From a therapeutic perspective, molecular classification is important, as it reduces the heterogeneity of patient groups and increases the likelihood of response to therapy. [5] There are two clear examples of this in breast cancer, from single-gene marker studies. The first, and perhaps most important finding in the biology of breast cancer was the class distinction between ER positive and negative tumors. Across populations of breast cancer patients, it is clear that ER positive tumors respond to anti-estrogen therapy, while ER negative tumors do not [6-9]. A second example is that of HER2 gene amplified tumors, which have been shown to respond preferentially to the anti-HER2 monoclonal antibody, trastuzumab (Herceptin).[10] It is gratifying, then, that expression profiling is able to identify these subgroups, across platforms, and has further pointed out sets of genes that define these tumor types. These subgroups are currently defined by cell lineage (luminal, basal) and the presence of the HER2 oncogene (HER2 enriched). The luminal tumors are divided into luminal A, and luminal B. While the initial study of Perou et al used several hundred genes to classify the tumor subtypes, this group has recently distilled the classification to only 50 genes (termed the PAM50) [11]. In addition, they showed that the subtypes predict sensitivity to particular therapies. Furthermore, our recent analysis of a taxane monotherapy trial (CALGB 9842/9840) suggests that molecularly-defined tumor subtypes differ in their response to this commonly used chemotherapy agent. [12]

Responses of Breast Cancer Subtypes to Current Therapies
HER2-enriched Subtype

The HER2 tumor subtype is more sensitive to anthracycline-containing chemotherapy and may be less sensitive to alkylating agents and agents which produce DNA adducts such as Cisplatinum and Oxaliplatinum. [13-15] In addition, recent studies suggest that HER2 tumors are preferentially sensitive to taxanes. [16] There is evidence that HER2 targeted therapy can reverse drug resistance in this tumor subtype, which has led to the development of specific regimens which take advantage of this synergistic effect between HER2 antibodies and most chemotherapy regimens tested. [17, 18]

Luminal A and B Subtypes

Luminal tumors are driven, at least in part, by estrogen receptor signaling. However, it has long been appreciated that ER positive tumors vary in their response to anti-estrogens (eg. tamoxifen, aromatase inhibitors). One of the striking findings from the molecular classification of Luminal A and B tumors is that a set of genes (including ER) is overexpressed in ER positive tumors that are particularly sensitive to anti-estrogens and these genes are characteristic of the Luminal A subtype. Luminal B tumors express some of the genes in this 'estrogen signature' but typically have lower expression of ER, lack of expression of many signature genes and higher levels of proliferation genes. In addition, Luminal B tumors are more likely to express other growth factor receptors, are less sensitive to anti-estrogens and more sensitive to chemotherapy (8, 9). This information has profound implications for treatment decision-making and provides novel targets for this breast tumor subtype (see below).

Basal-like Subtype

A new subgroup of breast cancer, now termed the 'basal-like' or 'triple-negative' subtype, has emerged from microarray profiling studies. This tumor type is molecularly distinct from other breast cancers, expressing one or more of the basal cytokeratins (CK 5/6, CK 14, CK903) and carries a worse outcome cancer, with up to 50% of these patients relapsing and dying of their breast cancer, even in early stages of disease. [1,4].

These breast cancers are insensitive to receptor-directed inhibitors (tamoxifen, anti-HER2 therapy), which may explain the worse prognosis associated with this tumor type across multiple breast cancer datasets. As noted above some basal tumors are likely to be taxane resistant. [19] However, the recently discovered 'achilles heel' of this tumor subtype may lie in the fact that these tumors appear to be deficient in the homolgous recombination/repair (HSR) pathway, due to loss of BRCA1 activity. [20, 21] Indeed, the tumors from BRCA1 carriers are nearly always triple negative (basal-like) and profile within the same group as sporadic basal tumors. The working hypothesis by many groups is that basal breast tumors are more sensitive to agents which induce DSBs such as cisplatin.

Symposium 2:

New Targets and Targeted Therapy for Breast Cancer Subtypes

HER2-enriched Subtype

The recognition of the pathogenic role of the HER2 oncogene in breast cancer led to the first highly successful targeted therapy (trastuzumab, Herceptin®) that began with a scientific discovery (22, 10). This success story has demonstrated that biologic insights into the mechanism of breast cancer pathogenesis can lead to cures for our patients. In addition, the importance of this target has been proven time and again as newer HER2-targeted therapies continue to show high levels of activity in this breast cancer subtype (eg. lapatinib, pertuzumab, neratinib, TDM-1). Furthermore, therapies that target the pathways which are important in HER2 pathogenesis are also meeting with success (eg. HSP-90 inhibitors, HDAC inhibitors). Finally, mechanisms of resistance to HER2 targeted therapy are predicted by known signal transduction pathways and alternative growth factor receptors. [23, 24, 25] The 'HER2 paradigm' demonstrates the success of the bench to bedside approach and gives hope and direction to scientists, clinicians and patients.

Luminal A and B Subtypes

While the 'HER2 paradigm' demonstrates the importance of the bench-to-bedside approach in developing targeted therapy, the first targeted therapy in breast cancer are the anti-estrogens in ER/PR positive tumors, and reminds us of the importance of clinical observation. This class of drugs has been used for over 5 decades, based on the observation that a subset of breast tumors could be successfully treated by estrogen withdrawal using oophorectomy, adrenalectomy or hypophysectomy. It was not until the 1970's that it was clearly appreciated what the target of these maneuvers was, ie the estrogen and/or progesterone receptors. The Luminal A and B subtypes represent the molecular phenotype that further refines this classification, and provides important insights into variability in response to anti-estrogens in so-called ER/PR positive tumors. As noted above, the Luminal A subtype is highly sensitive to anti-estrogens with corresponding expression of genes which characterize the 'estrogen signature'. The Luminal B tumors are less sensitive to anti-estrogens and have higher grade, proliferation and chemosensitivity. In addition, this subclass was discovered to have many other growth factor receptors (eg. c-MET, c-KIT, PDGFR, HER1-4) which provide numerous druggable targets. While the attempts to overcome anti-estrogen resistance with the addition of targeted therapy against these receptors has not been entirely successful, recent studies suggest that molecular profiling may be critical for understanding which tumors are most likely to benefit from this approach. Specifically, co-targeted of ER and EGFR with tamoxifen and gefitinib respectively was not a successful approach in the neoadjuvant setting [26], however more recent studies with lapatinib and letrozole suggest that the Luminal B subtype is most likely to benefit from this approach [27]. In addition, a recent Phase II study showed highly promising activity of anastrazole combined with the multi-targeted kinase inhibitor sorafenib in aromatase-inhibitor resistant metastatic breast cancer [28].

Basal-like Subtype

Perhaps the most feared breast cancer subtype is the 'basal-like' tumor which lack the classic ER, PR and HER2 receptors, is virtually always poorly differentiated, angiogenic and shows a very poor outcome in older cohort studies without treatment. It is important to recognize, however, that many basal-like tumors are exquisitely sensitive to chemotherapy as evidenced by preoperative studies showing the highest pathologic complete response rate and excellent overall survival if pCR is achieved. [21] However, there is clearly a subgroup of basal-like tumors that have a poor prognosis despite chemotherapy and enormous efforts have been made to discover the 'targets' for this group. In fact, the biologic insights from molecular profiling have played a critical role in the recent discovery and development of PARP inhibitors for basal-like breast cancer. As noted above, it was observed shortly after the definition of molecular subtypes that BRCA1 carriers almost always developed triple negative tumors and that these tumors profiled with the sporadic basal-like tumors. This led to the hypothesis that basal tumors were likely to be deficient in homologous recombination (HSR) as this DNA repair defect is characteristic of BRCA1 deficiency. Recent studies suggest that BRCA1 deficient cells may be particularly sensitive to PARP inhibitors as these agents are able to disable the single-strand break repair pathway and this, coupled with the double-strand break repair defect in BRCA1 deficient tumors leads to so-called synthetic lethality. [20, 29, 30] Although germ line mutations in BRCA1 account for the majority of dominantly inherited breast cancers, sporadic breast carcinomas rarely show mutations in the BRCA1 gene. [31] Interestingly, decreased BRCA1 expression has been observed in sporadic breast cancers correlating with higher tumor grade and poor prognosis, the basal-like subtype.[32,33] In this case, BRCA1 loss may be a result of epigenetic silencing of the BRCA1 promoter, or perhaps other mechanisms of BRCA downregulation, such as hypoxia which leads to decrease in BRCA1, RAD51 and other HSR pathway members.[34] Hence, the loss of BRCA1 appears to be associated with this tumor subtype, further supporting the contention that triple negative breast cancer is deficient in HSR, a fact that has been exploited clinically with the use of cisplatin and PARP inhibitors.

Summary

Understanding of the basic biology and molecular profiles of breast cancer has led to important insights into the optimal treatment for patients. This has led to cures for patients suffering from this devastating disease and gives hope for the future development of new targeted therapy for breast cancer.

Symposium 3-1:

Speaker: **Napoleone Ferrara, MD**
Genentech Fellow, Dept. of Molecular Oncology, Genentech
South San Francisco, USA
Director, Edwin L. Steele Laboratory for tumor Biology, Department of Radiation Oncology,
Massachusetts General Hospital,
Charlestown, MA, USA

Chair: **Chikashi Ishioka, MD**
Professor, Department of Clinical Oncology,
Tohoku University School of Medicine,
Japan

[Speaker's CV]

Napoleone Ferrara, M.D.
Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080
Phone: (650) 225-2968 Cell: (650) 303 8263 Fax: (650) 225-4265 E-mail: nf@gene.com
Date and place of birth: July 26, 1956; Catania, Italy Citizenship: USA and Italy

Positions held

Genentech Fellow Genentech, Inc.(May 2002-present)
Research Fellow •Cancer Research Institute •University of California, San Francisco. •San Francisco, CA (July 1986-June 1988)

Education

University of Catania Medical School, Catania, Italy (November 1974-February 1981) M.D. (cum laude) April 3, 1981
Liceo Classico "M. Cutelli" Catania, Italy (October 1969-July 1974) M. Classica, July 1974

Research interests and major accomplishments

The main research interests of my laboratory are the biology of angiogenesis and the identification of its regulators. In 1989 we reported the isolation and cDNA cloning of vascular endothelial growth factor (VEGF) and proposed that this molecule plays a unique role in the regulation of angiogenesis. My laboratory focused on the investigation of the molecular and biological properties of VEGF. In 1993 we reported that inhibition of VEGF by specific monoclonal antibodies results in suppression of growth of a variety of tumors in vivo. These findings represented the first direct evidence that inhibition of angiogenesis may block tumor growth. These work led to the development of a humanized anti-VEGF monoclonal antibody (bevacizumab; Avastin®) as a cancer therapy. Bevacizumab has been approved by the FDA for the treatment of metastatic colorectal cancer, non-small-cell lung cancer and metastatic breast cancer, in combination with chemotherapy. Also, we demonstrated that VEGF is an important mediator of angiogenesis associated with intraocular neovascular syndromes. These studies resulted in the clinical development of a humanized anti-VEGF Fab (Ranibizumab, Lucentis®), which was approved by the FDA in 2006 for the therapy of neovascular age-related macular degeneration. We are presently investigating mechanisms of tumor angiogenesis alternative to VEGF, in particular the role of factors produced by myeloid cells and fibroblasts.

Journal Editorial Board membership

•Angiogenesis; Cancer Research; Cardiac and Vascular Regeneration; Endothelium;
•Journal of Cardiovascular Pathobiology; Journal of Clinical Investigation; •Lymphatic Research and Biology; Science Translational Medicine.

Selected Committee Activities

•AACR Council of Scientific Advisers 2007 • Co-Chairperson, Program Committee AACR Annual Meeting 2008.
•Damon Runyon-Rachleff Innovation Award Committee Member. 2007-present.
•North Am. Vascular Biol. Org. (NABVO) Scientific Advisory Board Member (2010-).

Publications <Selected publications (ISI citations as of December 2009). >

1.Ferrara, N, Chen, H, Davis-Smyth, T, Nguyen, N, Gerber, H, Peers, D, Chisholm, V, Hillan, KJ, Schwall, R. Vascular endothelial growth factor is essential for corpus luteum angiogenesis. *Nature Med.* 3, 336-340, 1998. Cit.: 338.
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3.Gerber, HP, Malik, A, Solar, G, Sherman, D, Liang, XH, Meng, G, Hong, K, Marsters, JC, Ferrara, N. VEGF regulates haematopoietic stem cell survival by an internal autocrine loop mechanism. *Nature*. 417, 954–958, 2002. Cit.: 264.
4.LeCouter, J, Moritz, DR, Li, B, Phillips, GL, Liang, X-H, Gerber, HP, Hillan, KJ, Ferrara, N. Angiogenesis-independent endothelial protection of liver: Role of VEGFR-1. *Science*. 299, 890-893, 2003. Cit.: 227.
5.Ferrara, N, Gerber, HP, LeCouter, J. The biology of VEGF and its receptors. *Nature Med.* 9, 669-676, 2003. Cit.: 1905.
6.Hurwitz, H, Fehrenbacher, L, Novotny, W, Cartwright, T, Hainsworth, H, Helm, W, Berlin, J, Baron, A, Griffing, S, Holmgren, E, Ferrara, N, Fyfe, G, Rogers, B, Ross, R, Kabbinavar, F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N. Engl. J. Med.* 350, 2335-2342, 2004. Cit.: 2645.

Reviews and editorials

1.Ferrara, N. Retrospective- Binding to the extracellular matrix and proteolytic processing: two key mechanisms regulating VEGF action. *Mol. Biol. Cell.* In press.
2.Chung, AS, Ferrara, N. Targeting the tumor microenvironment with Src kinase inhibition. *Clin. Cancer Res.* In press.
3.Ferrara, N. Myeloid cells and angiogenesis. *Curr. Opin. Hematol.* In press
4.Chung, AS, Lee, J, Ferrara, N. Targeting the tumor vasculature: insights from physiological angiogenesis. *Nat. Rev. Cancer.* Submitted.
5.Ferrara, N. Angiogenesis. *Annu Rev. Cell Develop. Biol.* Vol. 27. In preparation.
6.The biology of EG-VEGF and Bv8 (prokineticins). *Endocr. Rev.* In preparation.
7.Ferrara, N. Role of VEGF in tumor angiogenesis. *Oncogene*. In preparation.

Book chapters

1.Ferrara, N, Gerber, HP. VEGF. In: Angiogenesis in cardiovascular disease. Ware, JA, Simons, M, Eds. Oxford Univ. Press. pp 101-127, 1999.
2.Ferrara, N, Gerber, HP. VEGF. Molecular and biological aspects. In: Advances in Organ Biology vol 7 - Coronary angiogenesis. Rakusan, K, Ed. JAI Press. pp 25-57, 1999.
3.Ferrara N. Targeting VEGF. In: Antiangiogenic Cancer Therapy.Davis, DW, Herbst, RS, Abruzzese, JA, Eds. CRC Press, pp 23-41, 2008.
4.Ferrara, N. Targeting VEGF to treat cancer and other disorders. In: Proc. 38th Intl. Symposium Princess Takamatsu Cancer Res. Fund. Nakagama, H,Dove WD, Mori, H, Wakabayashi, K, Eds, pp 162-166, 2008.
5.Ferrara N. Vascular endothelial growth factor. In: Encyclopedic Reference of Molecular Pharmacology. Springer, 2008.
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7.Ferrara, N. Signal transduction in tumor angiogenesis. In: Molecular Oncology: Causes of Cancer and targets for treatment. Gelmann, E, Sawyers, C,Rauscher, F, Eds. In preparation.
8.Ferrara, N. VEGF and pathological angiogenesis. In: Cancer Metastasis. Biologic Basis and: Therapeurics. Lyden, DC and Welch, D, Eds. In preparation.

Symposium 3-1:

-Prediction of response and tolerance of cacer drugs-

Targeting VEGF-A to treat cancer and other disorders

Napoleone Ferrara, MD
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Vascular endothelial growth factor (VEGF)-A is a well-characterized angiogenic factor involved in physiological and pathological growth of blood vessels. The tyrosine kinases Flt-1 (VEGFR-1) and Flk-1/KDR (VEGFR-2) are the main VEGF-A receptors. The importance of VEGF-A in vascular development is underscored by defective vascularization and embryonic lethality following inactivation of a single VEGF-A allele in mice. High expression of VEGF-A mRNA has been reported in many human tumors, including kidney, colorectal, lung, breast and several brain tumors, including the highly vascularized glioblastoma multiforme. Anti-VEGF-A monoclonal antibodies or other VEGF inhibitors block growth and neovascularization in tumor models. We developed a humanized anti-VEGF-A monoclonal antibody (bevacizumab). Bevacizumab has demonstrated clinical efficacy, including a survival advantage, in multiple tumor types. Bevacizumab has been approved by the USA Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer, non-small-cell lung cancer, metastatic breast cancer, renal cell carcinoma and glioblastoma multiforme. Numerous clinical trials testing bevacizumab in combination with the standard of therapy are underway in additional indications. Currently, efforts are ongoing to elucidate mechanisms of refractoriness/resistance to anti-VEGF therapies. Recent work from our laboratory identified myeloid cells and fibroblasts as sources of angiogenic factors potentially mediating tumor resistance to anti-VEGF. Furthermore, VEGF-A is implicated in intraocular neovascularization associated with active proliferative retinopathies and the wet form of age-related macular degeneration (AMD). A humanized anti –VEGF-A Fab (ranibizumab) has been developed for the treatment of the neovascular form of AMD. Ranibizumab administration maintained and even improved visual acuity.

Symposium 3-2:

Speaker: **Hasan Korkaya, DVM, PhD**
Laboratory of Max Wicha, MD
Research Investigator
Department of Internal Medicine
Comprehensive Cancer Center
University of Michigan, MI, USA

Chair: **Masakazu Toi, MD**
Professor, Breast Surgery Department
Kyoto University School of Medicine, Japan

[Speaker's CV]

Work

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Educational Qualifications

International Center for Genetic Engineering and Biotechnology (New Delhi/India). / 1999-2001(Year) / Ph.D. (Degree) /Molecular Biology(Subject)
Center for Biotechnology Jawaharlal Nehru University (New Delhi/India)./1996-1998(Year)/M.Sc. (Degree)/Biotechnology(Subject)
Faculty of Veterinary Medicine Istanbul University (Istanbul/Turkey)./1988-1993(Year)/DVM(Degree)/Veterinary Medicine(Subject)

Professional Experiences

Research Investigator/2008-(Year)/Cancer Stem Cell Research(Subject)
Research Fellow/2006-2008(Year)/Cancer Stem Cell Research(Subject)
Postdoctoral Research Fellow, Van Andel Research Institute Grand Rapids,MI/2002-2005(Year)/Cancer Research(Subject)

Publications

A. Research articles:

1. Madhuri Kakarala, Dean E. Brenner MD, **Hasan Korkaya**, Connie Cheng, Karim Tazi, Christophe Ginestier PhD, Suling Liu PhD, Gabriela Dontu and Max S. Wicha. Targeting Breast Stem Cells with the Cancer Preventive Compounds Curcumin and Piperine. Accepted in press. 2009. **Breast Cancer Research and Treatment.**
2. Christophe Ginestier, Suling Liu, Mark Diebel, **Hasan Korkaya**, Ming Luo, Marty Brown, Julien Wicikski, Olivier Cabaud, Emmanuelle Chrafe-Jauffret, Daniel Birnbaum, Jun-Lin Guan, Gabriela Dontu, Max S. Wicha. Targeting breast cancer stem cells through CXCR1 blockade. Accepted in press. 2009 **Journal of Clinical Investigation**
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4. Paul A. Bromann1, **Hasan Korkaya**1 and Sara A. Courtneidge. Src family kinases and receptor tyrosine kinases. **Oncogene** 2004 Oct 18;23:7957-68. (1 : First co-author)
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Technical Expertise:

•-DNA isolation, cloning and sequencing. •-Protein expression, purification and western blot analysis. •-Maintenance and propagation of animal and insect cells. •-Transfection, protein expression, metabolic labeling of recombinant proteins in eukaryotic cells. •-In vitro immune complex kinase assays. •-In vitro protein-protein interaction studies. •-Study of signal transduction pathways. •-Yeast two-hybrid analysis. •-mRNA isolation and ribonuclease protection assay (RPA). •-In vitro transcription assay (Run-off). •-Cellular proliferation assay. •-Microinjection of mammalian cells. •-Immunocytochemistry. •-Isolation of adult stem cells and maintenance in in vitro culture. •-in vivo mouse model of cancer stem cells. •-Humanization of mouse mammary fat pads for studying human mammary gland development.

Memberships to Scientific Organizations:

1. Turkish Biochemical Society, an adhering body to the International Union of Biochemistry and Molecular Biology (IUBMB).
2. TASSA (Turkish American Scientists and Scholar Association).
3. Elected Associate member of American Association for Cancer Research

References:

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-Prediction of response and tolerance of cacer drugs-

The role of PI3-K/Akt pathway in regulating the breast cancer stem cells and therapeutic resistance

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Despite recent advances in the treatment of breast cancer, the fact remains that once metastatic, the disease is incurable. We and others have provided strong support for the cancer stem cell (CSC) hypothesis which suggests that breast cancers are driven by a subpopulation of cells which display stem cell properties. Studies by our group and others have demonstrated a relative resistance of CSCs to chemotherapy and radiation therapy. One of the most significant advances in breast cancer therapeutics has been the development of HER2 targeted therapies for treatment of HER2 overexpressing breast cancers. Trastuzumab in the adjuvant setting has demonstrated significant impact on reducing tumor recurrence. However, one-third of HER2-positive tumors do not respond to HER2 targeted agents and resistance may develop in patients with chronic exposure. Studies have found that nearly 50% of patients who respond to HER2 targeted agents relapse within a year. Although the mechanism of resistance to HER2 targeted agents is not entirely clear, increasing evidence indicates that this resistance may be associated with loss of PTEN (phosphotase and tensin homolog), the gain of function of somatic mutations of PI3KA or truncation of the extracellular domain of HER2. We recently demonstrated in a set of breast cancer cell lines that trastuzumab-sensitive cell lines show decrease in CSC population, however the CSC population in resistant cell lines is not effected by trastuzumab suggesting a role in resistance.

We generated a mouse model for trastuzumab resistance utilizing engineered MCF7 cell lines overexressing HER2 or PTEN knockdown in addition to HER2 overexpression. PTEN deletion in HER2 expressing cells resulted in increased CSC population as compared to HER2 overexpression alone. PTEN deletion also increased the motility of cells by several fold in vitro. When we tested these cell lines for trastuzumab response in vitro, although the treatment of HER2 overexpressing cells decreased the CSC population had no effect in cell lines with PTEN deletion and HER2 overexpression. Our in vivo experiments demonstrated that PTEN deletion results in accelerated tumor growth and development of extensive metastasis from primary tumors, properties not found in parent or HER2 overexpressing MCF7 cells. We observed an extensive metastasis to liver in mice with primary tumor generated from PTEN deleted and HER2 overexpressing cells. We are in the process of analyzing the trastuzumab resistance and currently testing the combination of trastuzumab with Akt inhibitor in these mouse models and results will be discussed in the AACR annual meeting.

These studies suggest that the remarkable clinical efficacy of HER2 inhibitors may be due to their ability to target breast CSCs and combination of with other therapies such as Akt inhibitors may benefit patients with trastuzumab resistance.

Overview:

Speaker: **Eric Van Cutsem, MD, PhD**
Professor, Department of Internal Medicine, Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium

Chair: **Yuko Kitagawa, MD**
Professor, Department of Surgery, Keio University School of Medicine, Japan

[Speaker's Biographical Sketch]

Eric Van Cutsem is Professor of Internal Medicine at the University of Leuven, Belgium and is head of the Digestive Oncology department at the University Hospital Gasthuisberg in Leuven and is senior clinical researcher of Fund for Scientific Research in Flanders. He obtained his degree of MD and PhD at the university of Leuven and spent during his training several periods abroad: UK, Netherlands, Switzerland and USA.

He has a large clinical activity and is involved and/or leads many national and international clinical and translational research projects on gastrointestinal cancer.

Professor Van Cutsem has published more than 250 peer-reviewed articles in prestigious journals including New England Journal Medicine, Journal of Clinical Oncology, Lancet, Lancet Oncology, JAMA, Annals Oncology and European Journal of Cancer and also more than 400 other texts or chapters in books on gastrointestinal cancer. He is Co-Editor of the reference textbook on gastrointestinal cancer: Principles and Practice of Gastrointestinal Oncology: Second edition, 2008, and has been an editorial board member of numerous prestigious journals, including Journal of Clinical Oncology, Annals of Oncology, and European Journal of Cancer.

Professor Van Cutsem is a member of several scientific organizations, including the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), European NeuroEndocrine Tumour Society (ENETS) and many national organizations. He is/was a member of the Scientific Program Committee and/or educational committee for ASCO, ASCO-GI cancers symposium, ESMO and ECCO. Professor Van Cutsem is also a member of the ESMO faculty and of the strategic ESMO Multidisciplinary Oncology Committee.

He served as Secretary of the European Organisation for Research and Treatment of Cancer – Gastrointestinal Cancer (EORTC-GI) group from January 2000 to 2003, and was Chair of the EORTC-GI group from 2003 to 2007 and is chairman of PETACC (Pan-European Trials on Adjuvant Colon Cancer) since 2008 and board member of the EORTC since 2009. He is also chairman of the governmental colon cancer prevention task force in Belgium and is president of FAPA (Familial Adenomatous Polyposis Association).

Eric Van Cutsem has been founder of and is chair of the Scientific Committee of the World Congress on Gastrointestinal Cancer in Barcelona since June 2004 (in partnership with ESMO since 2005).

Overview:

The role of targeted agents in the management of metastatic in colorectal cancer

Eric Van Cutsem, MD, PhD
Digestive Oncology Unit, University Hospital Gasthuisberg, 3000 Leuven, Belgium

The management of patients with metastatic colorectal cancer (CRC) has changed dramatically over the last years, with increasing chances of prolonged survival. The median survival of patients with unresectable metastatic disease approaches now 24 months. The development of new cytotoxic and targeted agents, as well as the multidisciplinary management of patients with resectable and initially non-resectable metastases contribute to the progress. The development of the cytotoxic agents irinotecan, oxaliplatin and capecitabine and of the biological agents bevacizumab, cetuximab and panitumumab has clearly increased the therapeutic options for patients with metastatic colorectal cancer. Several other new agents are far advanced in development in colorectal cancer.

There is a strong preclinical and clinical rationale for the use of Vascular Endothelial Growth Factor (VEGF) inhibitors in colorectal cancer. The anti-VEGF monoclonal antibody, bevacizumab, increases the activity of a variety of active cytotoxic regimens in metastatic CRC. It has been shown to increase the activity of a variety of active cytotoxic regimens in the first line treatment of metastatic CRC: 5-fluorouracil (5-FU)/leucovorin, capecitabine, irinotecan- and oxaliplatin-based regimens. Bevacizumab also increases the activity of FOLFOX (5-FU/LV/oxaliplatin) in second-line treatment.

Aflibercept (VEGF trap) is engineered soluble receptor made from extracellular domains of VEGFR1 and VEGFR1 and binds to all isoforms of VEGF and to placental growth factor. Aflibercept is under active investigation in phase 3 in combination with standard cytotoxic combinations in metastatic CRC. Several small molecule VEGFR tyrosine kinase (e.g. cediranib, sunitinib, axitinib) are actually in phase 3 development in combination with standard combination cytotoxic regimens in metastatic CRC.

The activity of the anti-epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab has been shown initially in chemotherapy refractory metastatic CRC. The combination of cetuximab with irinotecan is more active in this setting than cetuximab alone. The activity of anti-EGFR antibodies is confined to patients with a KRAS wild type tumour. Recent data showed also an increased activity of cetuximab and panitumumab in combination with chemotherapy in less advanced stages of metastatic CRC. The activity of the anti-EGFR antibodies is confined to patients with a KRAS wild type tumour and it is known that ± 60 % of colorectal cancers are KRAS wild type tumours.

Many *open questions and challenges* remain in relation to the use of the anti-VEGF and anti-EGFR antibodies in metastatic CRC. Answers are needed to optimize the outcome for patients and the more optimal use of the resources. A crucial challenge is to demonstrate which patients are more likely to respond to bevacizumab-containing regimens and to the anti-EGFR antibodies cetuximab and panitumumab. Validated predictive for angiogenesis inhibitors are not yet available. Amongst the markers under investigation are Single Nucleotide Polymorphisms (SNP's). The data on KRAS as a predictor marker for resistance to anti-EGFR antibodies open new perspectives for the development of other predictive markers and also for the classification of metastatic CRC according to KRAS status. Emerging markers are BRAF, PI3K and the ligands amphi- and epiregulin.

A second important challenge is the strategic question on the best combination, on the best sequence and on the most optimal use of the different cytotoxic agents in combination with the biologicals in CRC. Amongst other relevant clinical questions are questions on the optimal duration of bevacizumab, on the continuation of bevacizumab after progression, on the significance of skin rash in patients treated with anti-EGFR antibodies and on the real impact of bevacizumab and cetuximab in the neoadjuvant preoperative treatment of liver metastases. An important challenge is the understanding of the mechanism why tumours that initially respond to a combination of cytotoxics and biologicals may become resistant to this combination.

In conclusion: the management of patients with advanced colorectal cancer has improved. The angiogenesis inhibitor, bevacizumab, as well as the EGFR-inhibitors have clearly increased the therapeutic armentarium of patients with metastatic colorectal cancer. The introduction of the new agents offer also prospects for an increased chance of a longer survival for patients with metastatic colorectal cancer. The major challenge is now to implement strategies in which patients can be selected, based on molecular characteristics and/or pharmacogenomic profiles so that the new drugs and the resources can be used optimally for our patients with metastatic colorectal cancer.

Review and Consensus Meeting: *by all participants*

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Co-Chair:

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memo

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