
Martine J. Piccart – William C. Wood – Chie-Mien Hung
Lawrence J. Solin – Fatima Cardoso (Eds.)

Breast Cancer and Molecular Medicine

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Martine J. Piccart, MD, PhD

Dept. of Medical Oncology
Jules Bordet Institute
Boulevard de Waterloo, 215
1000 Brussels
Belgium
Martine.piccart@bordet.be

Mien-Chie Hung, PhD

The University of Texas MD
Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030-4095
USA
mhung@mdanderson.org

Lawrence J Solin, MD

Dept. of Radiation Oncology
Hospital of the University of
Pennsylvania
3400 Spruce Street
Philadelphia, Pennsylvania
19104-4283
USA
solin@xrt.upenn.edu

Fatima Cardoso, MD

Dept. of Medical Oncology
Jules Bordet Institute
Boulevard de Waterloo, 125
1000 Brussels
Belgium
Fatima.cardoso@bordet.be

William Wood, MD

Dept. of Surgery
Emory University Hospital
1364 Clifton Road NE B206
Atlanta, Georgia 30322-1059
USA
William_wood@emory.org

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Foreword

LAWRENCE J. SOLIN, WILLIAM WOOD, FATIMA
CARDOSO, MIEN-CHIE HUNG, AND MARTINE PICCART

Why should you buy another book on breast cancer? Don't you already have enough breast cancer books on your shelf? As editors, we have attempted to create a different kind of breast cancer book. Although the typical breast cancer book is written as a compendium of diagnoses and treatments, the focus of this book is on the present and future of breast cancer research and treatment, with an emphasis on translational research. Breast cancer treatment is moving increasingly toward laboratory-based, targeted therapies that are tailored to the individual patient. The treatment of breast cancer, and probably all cancers, will likely soon be practiced in this radically different fashion. The tsunami wave of laboratory and translational research that is already under way will soon alter the management of breast cancer in fundamental ways, and in fact, is already influencing the way in which we think about treating breast cancer patients and performing research.

Research into clinical, laboratory, and translational aspects of breast cancer has improved enormously our ability to treat and cure patients with this disease. Population-based data (for example, from the USA and the UK) document a substantial decrease in the mortality from breast cancer in the last decade, notwithstanding an increase in the incidence of breast cancer detection, attesting to the benefit in human terms from this research. We believe that this downward trend in mortality is only the beginning.

What makes this book unique is that it considers a wide range of relevant and exciting areas of clinical, translational, and basic research for their potential for clinical application today as well as for transforming future breast cancer treatment. If the history of scientific discovery is any guide, then some, but not all, of these research areas will prove valuable for patient care, and the remainder will fall by the wayside. However, no one can predict today which of these research areas will have the most impact on treating patients in the years to come.

The last 25 years of clinical research have been characterized by large, randomized trials that have led to improved outcomes for populations of women. Some of these trials have addressed differing treatment concepts, and others, different regimens of similar therapy. Overviews and meta-analyses have uncovered major trends. However, for any given trial, only some of the patients will derive the benefit from treatment that is nevertheless applied to the overall group of patients. A limitation of comparing large populations of patients is that some subgroups may be too small to be properly evaluated. While such large clinical trials have improved demonstrably the outcome for the overall group, this approach may do so by overtreating some patients while undertreating others.

With the growing recognition of the large heterogeneity of breast cancer patients, breast cancer treatment is becoming increasingly individualized. The observation that each patient is unique, recognized clinically for decades, is now being confirmed by the genetic analysis of individual tumor DNA specimens. The genetic individuality of tumors strongly supports the clinical trend toward increasingly individualized treatment for each patient.

Today, laboratory-based research is expanding, with the potential to translate into clinically valuable improvements. The most basic and elemental processes are understanding cancer genes, how these genes work, the products and mechanisms of altered cellular functions, and the relationship between cancer cells and normal cells. Laboratory research is fueling our understanding of cancer cell biology. With this research come insights into potential targets to exploit and new targeted therapies to employ. Individually designed combinations of therapies will soon become the norm, and currently available antineoplastic treatments (chemotherapeutic, hormonal, biologic, radiotherapeutic, and surgical) will be used more strategically. Today's translational research presages a new era in which therapies may ultimately be tailored to the most elemental basis of the individual tumor in the individual patient.

Historically, classifying patients into broad groups has facilitated the development of treatment guidelines. "Lumping" patients into broad categories of disease (for example, based on nodal positivity, stage, or hormone receptor status) and "splitting" patients based on individual patient and tumor characteristics both play an important role in the conceptual framework for managing breast cancer patients. For example, lumping patients into so-called early-stage disease guides local-regional management of breast-conservation treatment versus mastec-

tomy, whereas lumping patients into so-called locally advanced breast cancer guides the treatment decision toward neoadjuvant chemotherapy. Nonetheless, the paradigm of broadly grouping patients to guide treatment decisions may soon undergo radical change.

Our increasingly sophisticated understanding of breast cancer is forcing us to recognize substantial clinical heterogeneity, even within predefined patient groups, and to reevaluate our concepts of patient management strategies. Thus, splitting or separating the patients into smaller subgroups of patients has become a widely accepted practice, and tailoring treatment in this fashion has emerged as a rational treatment strategy. Translational research has become the driving factor for much of this change in our approach toward treatment strategies. Furthermore, as the basic principles of cancer biology drive translational efforts into more effective clinical treatment strategies, clinical problems are also driving laboratory-based research to solve these problems.

Many examples could be given to demonstrate translational research findings that have already altered clinical practice today. The use of tamoxifen as a hormonal agent represents a major shift in the systemic management of breast cancer patients, and innumerable women have been cured through the use of this very well tolerated drug. However, the most effective clinical use of tamoxifen takes into account the heterogeneity of patient presentations. After research studies demonstrated the importance of estrogen and progesterone receptors, clinicians were able to determine the appropriate subgroup of tumors (hormone receptor positive) that should be treated with adjuvant tamoxifen. In this way, tamoxifen became the first systemic agent used for targeted breast cancer treatment.

Although uncommon, the clinically observed side effects of tamoxifen can potentially be severe, even life-threatening, and have consequently stimulated laboratory research into developing more specific agents with fewer side effects. Two major groups of new agents have been developed: (1) the selective estrogen receptor modulators (SERMs), and (2) the aromatase inhibitors (AIs). SERMs and AIs may have the same, or an even higher, benefit as tamoxifen for preventing recurrence of disease, but with a lower risk of side effects. These agents are also not without side effects, and so even newer agents continue to be developed for clinical testing.

The AIs have been evaluated in several studies and are challenging tamoxifen as the gold standard both for metastatic disease and in the adjuvant setting. The Arimidex, Tamoxifen Alone or in Combination (ATAC) trial demonstrated an improved dis-

ease-free survival (DFS) and toxicity profile for women treated with anastrozole. The National Cancer Institute of Canada MA 17 trial reported an improved DFS for women receiving 5 years of letrozole after completing a 5-year course of tamoxifen, raising the hypothesis that a prolonged duration of more than 5 years of adjuvant hormonal therapy may be beneficial. In the Intergroup Exemestane Study, an improved DFS was found for the combination of tamoxifen followed by exemestane for a total of 5 years compared to tamoxifen alone for 5 years.

The hereditary breast cancer story is another example of a clinical observation driving translational research. In the not too distant past, it was commonly observed that “breast cancer runs in families.” The power of this clinical observation was channeled into the laboratory finding of specific breast cancer genes associated with hereditary breast cancer. To date, two major genes (BRCA1 and BRCA2), as well as other genes, have been associated with an increased risk of developing breast cancer. Several hereditary breast cancer syndromes have been identified, and the potential exists for identifying additional genes responsible for these breast cancer syndromes.

The ability to use rapid and reliable testing to identify women with specific BRCA mutations has promoted the development of improved management strategies for these patients. The available options today for such patients include a number of tailored strategies, such as prophylactic surgery (for example, bilateral oophorectomies or bilateral mastectomies), systemic agents for breast cancer prevention (for example, tamoxifen), or heightened surveillance (for example, breast cancer screening using magnetic resonance imaging, MRI, in addition to conventional mammography).

The impact of research on clinical practice is not limited to systemic therapies. Many research developments have influenced local-regional treatments and their integration with systemic therapies. For example, improved imaging allows for more accurate surgery. MRI has become part of routine clinical practice, as it is complementary to conventional imaging studies. MRI of the breast may have a role in any number of clinical scenarios, such as improving the definition of the tumor volume, monitoring the response to neoadjuvant chemotherapy for locally advanced breast cancer, more accurate staging of the breast for potential candidates for breast-conservation treatment with early stage disease, and differentiating scar from local recurrence in follow-up after breast-conservation treatment.

The integration of computed tomography (CT) and MRI into radiation oncology treatment planning has become routine in

clinical practice. Furthermore, the integration of high-speed computers has facilitated the delivery of targeted radiation treatment that can increase the radiation dose to the tumor (or target) and decrease the dose to normal tissues, with a corresponding reduction in toxicity. The ability to cover the target volume (for example, the intact breast) while omitting critical normal tissues (for example, the heart and coronary vessels) maintains tumor control, but without the late toxicities that were seen in older studies. One can easily envision even further refinements in local-regional treatment that incorporate the ongoing developments in radiologic imaging.

The future of translational research cannot be predicted. Many, but not all, of the promising strategies explored in this textbook will prove clinically valuable in the years to come. While some of these approaches have already reached the clinic and have made a tremendous impact on patient management today, many strategies, although highly promising, remain to show clinical utility. “Bench to bedside” and “bedside to bench” research for breast cancer is an exciting dynamic that has only just begun to yield valuable results.

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Contributors

David Abramson

Department of Surgery
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10023
USA
E-mail: abramsod@mskcc.org

Kathy S. Albain

Loyola University Medical Centre
Cardinal Bernardin Cancer Centre
2160 S First Avenue Rm 109
Maywood, IL 60153
USA
E-mail: kalbain@lumc.edu

Douglas W. Arthur

Dept. Radiation Oncology
Virginia Commonwealth University
Richmond, VA 23298-0058
USA
E-mail: DArthur@mcvh-vcu.edu

Evandro Azambuja

Department of Medical Oncology
Jules Bordet Institute
Boulevard de Waterloo, 125
1000 Brussels
Belgium
E-mail: evandro.azambuja@bordet.be

Jose Baselga

Department of Medical Oncology
Vall D'Hebron University Hospital
P Vall o Hebron 119-129
Barcelona 08035
Spain
E-mail: baselga@hg.vhebron.es

Wendie Berg

American Radiology Services, Inc.
John Hopkins Greenspring
301 Merrie Hunt Drive
Lutherville, MD 21093
USA
E-mail: wendieberg@hotmail.com

Chantal Benard-Marty

Department of Medical Oncology
Jules Bordet Institute
Boulevard de Waterloo, 125
1000 Brussels
Belgium
E-mail: chantal.bernard@bordet.be

Hyman Bernard Muss

UHC St Joseph 3400
University of Vermont
1 S Prospect Street
Burlington, VT 05401-1473
USA
E-mail: hyman.muss@vtmednet.org

Ephi Betan

Georgia School of Professional Psychology
Clinical Psychology Department
Argosy University/Atlanta
980 Hammond Drive
Suite 100
Atlanta, GA 30328
USA
E-mail: ebetan@argosyu.edu

Jean-Jacques Body

Institut Jules Bordet
1, rue Héger-Bordet
1000 Brussels
Belgium
E-mail: jj.body@bordet.be

Jan Bogaerts

EORTC Data Centre
Avenue E Mounier 83/Boîte 11
Brussels 1200
Belgium
E-mail: jbo@eortc.be

Angela Bowling

Emory University School of Medicine
Atlanta, GA
USA
E-mail: tittlemouse25@hotmail.com

Ebony Boyce

Laboratory of Pathology
National Cancer Institute
Bethesda, MD
USA

Grant Walter Carlson

Emory Clinic
1365B Clifton Rd NE
Atlanta, GA 30322-1013
USA
E-mail: grant_carlson@emory.org

Fatima Cardoso

Department of Medical Oncology
Jules Bordet Institute
Boulevard de Waterloo, 125
1000 Brussels
Belgium
E-mail: fatima.cardoso@bordet.be

Clifford K.S. Chao

Department of Radiation Oncology
UT MD Anderson Cancer Center
1515 Holcombe Boulevard
Houston, TX 77030
USA
E-mail: cchao@mail.mdanderson.org

Alan Stuart Coates

Australian Cancer Society
GPBO Box 4708
Sydney, NSW 2001
Australia
E-mail: alancoates@cancer.org.au

Javier Cortes

Oncology Service
Vall D'Hebron University Hospital
P Vall o Hebron 119-129
Barcelona 08035
Spain
E-mail: cortes@hg.vhebron.es

Yukun Cui

Department of Molecular and Cellular Biology
Baylor College of Medicine
MS: BCM600, 1220 Alkek
One Baylor Plaza
Houston, TX 77030
USA
E-mail: ycui@breastcenter.tmc.edu

Steven A. Curley

Department of Surgical Oncology
UT MD Anderson Cancer Center
1515 Holcombe Boulevard Box 424
Houston, TX 77030
USA
E-mail: scurley@mdanderson.org

Lissandra Dal Lago

Department of Medical Oncology
Jules Bordet Institute
Boulevard de Waterloo, 125
1000 Brussels
Belgium
E-mail: lissandra.dallago@bordet.be

Nancy Davidson

The Sidney Kimmel Comprehensive Cancer Center at Johns
Hopkins
Cancer Research Building, Room 409
1650 Orleans Street
Baltimore, MD 21231
USA
E-mail: davidna@jhmi.edu

Mellar P. Davis

Hematology/Medical Oncology
9500 Euclid Avenue
Cleveland Clinic Foundation
Cleveland, OH 44195
USA
E-mail: davism6@ccf.org

Chi-Ping Day

Bldg. 37, Room 5002
NIH/NCI-Bethesda
Bethesda, MD 20892-4264
USA
E-mail: daychi@mail.nih.gov

Gaston Demonty

Translational Research Unit
Jules Bordet Institute
Boulevard de Waterloo, 215
1000 Brussels
Belgium
E-mail: Gaston.Demonty@bordet.be

Christine Desmedt

Translational Research Unit
Jules Bordet Institute
Boulevard de Waterloo, 215
1000 Brussels
Belgium
E-mail: Christine.Desmedt@bordet.be

Daniel Devriendt

Department of Radiation Therapy
Institut Jules Bordet
Université Libre de Bruxelles
Brussels
Belgium
E-mail: daniel.devriendt@bordet.be

Virginie Durbecq

Translational Research Unit
Jules Bordet Institute
Boulevard de Waterloo, 215
1000 Brussels
Belgium
E-mail: Virginie.Durbecq@bordet.be

Vlatka Duric

NHMRC Clinical Trials Centre and Department of Psychological Medicine, University of Sydney
NHMRC Clinical Trials Centre
Locked Bag 77
Camperdown, NSW 2050
Australia
E-mail: vlatka@ctc.usyd.edu.au

Jan Erik Duus

Champlain Valley Physicians Hospital
Fitzpatrick Cancer Center
75 Beekman St.
Plattsburgh, NY 12901
USA
E-mail: jduus1@alum.rpi.edu

Matthew James Ellis

660 South Euclid
Campus Box 8056
St. Louis, MO 63110
E-mail: mellis@im.wustl.edu

Paul Anthony Ellis

Guys Hospital
St Thomas Street
London SE1 9RT
UK
E-mail: paul.ellis@gstt.sthames.nhs.uk

Alexandru E. Eniu

Cancer Institute “I. Chiricuta”
Department of Breast Tumors
Republicii 34–36
400015 Cluj-Napoca
Romania
E-mail: aleniu@iocn.ro

Laura Esserman

Breast Care Center NCSF
University of California San Francisco
1600 Divisadero Street, 2nd Floor
San Francisco, CA 94115-3006
USA
E-mail: laura.esserman@ucsfmedctr.org

Ian S. Fentiman

Guy's King's & St Thomas' School of Medicine
Guy's Hospital
London SE1 9RT
UK
E-mail: ian.fentiman@cancer.org.uk

Alain Fourquet

Department of Radiation Oncology
Institut Curie
26 Rue d'Ulm
75005 Paris
France
E-mail: alain.fourquet@curie.net

Suzanne A.W. Fuqua

Breast Center
Baylor College of Medicine
MS: BCM600, 1220 Alkek
One Baylor Plaza
Houston, TX 77030
USA
E-mail: sfuqua@bcm.tmc.edu

Daniele Generali

Molecular Oncology
Cancer Research UK
Weatherall Institute of Molecular Medicine
John Radcliffe Hospital
Oxford OX3 9DS
UK
E-mail: daniele.general@cancer.org.uk

Sharon H. Giordano

Department of Breast Medical Oncology
UT MD Anderson Cancer Center
1515 Holcombe Boulevard Box 424
Houston, TX 77030
USA
E-mail: sgiordan@mdanderson.org

Marjorie C. Green

Department of Breast Medical Oncology
UT MD Anderson Cancer Center
1515 Holcombe Boulevard Box 424
Houston, TX 77030
USA
E-mail: mgreen@mdanderson.org

Bruce Haffty

Department of Radiation Oncology
The Cancer Institute of New Jersey
195 Little Albany Street
New Brunswick, NJ 08903
USA

Anne Hamilton

Level 6, Gloucester House
Royal Prince Alfred Hospital
Missenden Road
Camperdown, NSW 2050
Australia
E-mail: anne.hamilton@cs.nsw.gov.au

Jonathan A.F. Hannay

Department of Surgical Oncology
Box 107
MD Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030
USA
E-mail: jahannay@manderson.org

Adrian L. Harris

Molecular Oncology
Cancer Research UK
Weatherall Institute of Molecular Medicine
John Radcliffe Hospital
Oxford OX3 9DS
UK
E-mail: aharris.lab@cancer.org.uk

George Hildebrand

Department of Medicine
Hôpital Erasme
Route de Lennik, 808
1070 Brussels
Belgium
E-mail: hildebrand@skynet.be

Chris E. Holmes

1 Colchester Avenue, ST. Joseph 3rd floor
Department of Hematology and Oncology
University of Vermont - FAHC
Burlington, VT 05401
USA
E-mail: chris.holmes@vtmednet.org

Gabriel N. Hortobagyi

Department of Breast Medical Oncology
UT MD Anderson Cancer Center
1515 Holcombe Boulevard Box 424
Houston, TX 77030
USA
E-mail: ghortoba@mdanderson.org

Clifford Hudis

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021-6007
USA
E-mail: hudisc@mskcc.org

Mien-Chie Hung

The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030-4095
USA
E-mail: mhung@mdanderson.org

Tara L. Huston

Department of Surgery
New York-Presbyterian Hospital
Weill Cornell Medical Center
435 East 70th Street
New York, NY 10021
USA
E-mail: taa9002@nyp.org

Rachel M. Jones

Department of Medical Oncology
South West Wales Cancer Institute
Singleton Hospital
Sketty, Swansea SA2 8QA
UK
E-mail: rachelm.Jones@swansea-tr.wales.nhs.uk

V. Craig Jordan

Fox Chase Cancer Center
Department of Surgery
333 Cotman Ave
Philadelphia, PA 19111-2497
USA
E-mail: v.craig.jordan@fccc.edu

Elise C. Kohn

Laboratory of Pathology
National Cancer Institute
Bethesda, MD
USA

Daniel Krauss

Department of Radiation Oncology
William Beaumont Hospital
3601 W. Thirteen Mile Road
Royal Oak, MI 48073
USA
E-mail: dkrauss@beaumont.edu

Ian Krop

Dana-Farber Cancer Institute
44 Binney St
Boston, MA 02115-6084
USA
E-mail: ikrop@partners.org

Hannah Larsen

1332-B Euclid Avenue
Emory University School of Medicine
Atlanta, GA 30307
USA
E-mail: hhlarsen@alum.emory.edu

Robert Leonard

Department of Medical Oncology
South West Wales Cancer Institute
Singleton Hospital
Sketty, Swansea SA2 8QA
UK
E-mail: r.c.f.leonard@swansea.ac.uk
E-mail: robert@swwci.vianw.co.uk
E-mail: helen.murphy@swansea-tr.wales.nhs.uk (secretary)

M. Levivier

Department of Neurosurgery
Hôpital Erasme
Route de Lennik, 808
1070 Brussels
Belgium

Edison T. Liu

Genome Institute of Singapore
Genome #02-01
60 Biopolis Street
Singapore 138672
Singapore
E-mail: liue@gis.a-star.edu.sg

Hui-Wen Lo

Department of Molecular and Cellular Oncology
The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030
USA
E-mail: hlo@mdanderson.org

Shelly S. Lo

Loyola University Medical Centre
Cardinal Bernardin Cancer Centre
2160 S First Avenue Rm 109
Maywood, IL 60153
USA
E-mail: shlo@lumc.edu

Sherene M. Loi

Translational Research Unit
Jules Bordet Institute
Boulevard de Waterloo, 215
1000 Brussels
Belgium
E-mail: Sherene.loi@bordet.be

Eleftherios P. Mamounas

Aultman Cancer Centre
2600 Sixth Street SW
Canton, OH 44710
USA
E-mail: tmamounas@aultman.com

Beryl McCormick

Department of Radiation Oncology
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021
USA
E-mail: mccormib@mskcc.org

Philip Meijnen

Department of Surgery
Antoni van Leeuwenhoek Hospital
Amsterdam Netherlands Cancer Institute
Plesmanlaan 121
1066 CX Amsterdam
The Netherlands
E-mail: p.meijnen@nki.nl

Gordon B. Mills

Molecular Therapeutics
MD Anderson Cancer Center
1515 Holcombe Boulevard T-5-3900
Houston, TX 77030
USA
E-mail: gmills@mail.mdanderson.org

Monica Morrow

Chairman, Department of Surgical Oncology
Fox Chase Cancer Center
Department of Surgery
333 Cotman Ave
Philadelphia, PA 19111-2497
USA
E-mail: monica.morrow@fccc.edu

Dominique Musselman

Emory University School of Medicine
Department of Psychiatry
Woodruff Memorial Building
1639 Pierce Drive, Suite 4000
Atlanta, GA 30322
USA
E-mail: dmussel@emory.edu

Larry Norton

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021-6007
USA
E-mail: nortonl@mskcc.org

Joyce O'Shaughnessy

US Oncology Group
3535 Worth St. Collins 5
Dallas, TX 75246
USA
E-mail: Joyce.OShaughnessy@usoncology.com

Catherine Park

Department of Radiation Oncology
University of California San Francisco
1600 Divisadero St.
San Francisco, CA 94143
USA
E-mail: park@radonc17.ucsf.edu

Edith A. Perez

Division of Hematology/Oncology
Multidisciplinary Breast Clinic
Mayo Clinic Jacksonville
4500 San Pablo Rd
Jacksonville, FL 32224-1865
USA
E-mail: perez.edith@mayo.edu

Johannes L. Peterse

Department of Pathology
Antoni van Leeuwenhoek Hospital
Amsterdam Netherlands Cancer Institute
Plesmanlaan 121
1066 CX Amsterdam
The Netherlands
E-mail: j.peterse@nki.nl

Martine J. Piccart

Department of Medical Oncology
Jules Bordet Institute
Boulevard de Waterloo, 215
1000 Brussels
Belgium
E-mail: martine.piccart@bordet.be

Kathleen I. Pritchard

Head Clinical Trial and Epidemiology
Toronto Sunnybrook Regional Cancer Center
2075 Bayview Avenue
Toronto, ON M4N 3M5
Canada
E-mail: kathy.pritchard@sw.ca

Tatiana M. Prowell

The Sidney Kimmel Comprehensive Cancer Center at Johns
Hopkins
Cancer Research Building, Room 186
1650 Orleans Street
Baltimore, MD 21231
USA
E-mail: tprowell@jhmi.edu

Kun-Ming Rau

123 Ta-Pei Road
Niao-Sung Hsiang
Kaohsiung Hsien
Taiwan
E-mail: kmrau58@adm.cgmh.org.tw

Alistair Ring

Department of Medical Oncology
Thomas Guy House
Guy's Hospital
London SE1 9RT
UK
E-mail: alastair.ring@gstt.nhs.uk

Anne de la Rochefordière

Department of Radiation Oncology
Institut Curie
26 Rue d'Ulm
75005 Paris
France
E-mail: anne.de-la-rochefordiere@curie.net

Eric Keith Rowinsky

Institute for Drug Development
Cancer Therapy and Research Center
7979 Wurzbach Road
4th Floor Zeller Building
San Antonio, TX 78229-3271
USA
E-mail: erowinsk@saci.org

Emiel J.T. Rutgers

Department of Surgery
The Netherlands Cancer Institute
Antoni van Leeuwenhoek Hospital
Plesmanlaan 121
Amsterdam 1066 CX
The Netherlands
E-mail: e.rutgers@nki.nl

Brigitte Siga-Zafrani

Department of Pathology
Institut Curie
26 rue d'Ulm
75005 Paris
France
E-mail: brigitte.segal@curie.net

Rache M. Simmons

New York-Presbyterian Hospital/Weill Cornell Medical Center
425 East 61st Street
New York, NY 10021
USA
E-mail: rms2002@med.cornell.edu

Lawrence J. Solin

Department of Radiation Oncology
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104-4283
USA
E-mail: solin@xrt.upenn.edu

Wendy Somerset

1355 Peachtree St, Suite 580
Emory University School of Medicine
Atlanta, GA 30309
USA
E-mail: wsomerset@gmail.com

Christos Sotiriou

Jules Bordet Institute
Boulevard de Waterloo, 121
1000 Brussels
Belgium
E-mail: christos.sotiriou@bordet.be

Martin Stockler

NHMRC Clinical Trials Centre
University of Sydney
Sydney, NSW
Australia
E-mail: stockler@med.usyd.edu.au

Steven C. Stout

Emory University School of Medicine
Department of Psychiatry and Behavioral Sciences
Woodruff Research Memorial Building, Suite 4000
Atlanta, GA 30322
USA
E-mail: sstout@emory.edu

Patrick Therasse

EORTC Data Centre
Avenue E Mounier 83/Boîte 11
Brussels 1200
Belgium
E-mail: pth@eortc.be

Mark van deVijver

Department of Pathology
Antoni van Leeuwenhoek Hospital
Amsterdam Netherlands Cancer Institute
Plesmanlaan 121
1066 CX Amsterdam
The Netherlands
E-mail: m.vd.vijver@nki.nl

Frank Vicini

Department of Radiation Oncology
William Beaumont Hospital
3601 W. Thirteen Mile Road
Royal Oak, MI 48073
USA
E-mail: fvicini@beaumont.edu

Shao-Chun Wang

Department of Molecular and Cellular Oncology
The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030
USA
E-mail: scwang@mdanderson.org

Timothy Whelan

Hamilton Regional Cancer Center
699 Concession St. Room 3-62
Hamilton, ON L8V 5C2
Canada
E-mail: tim.whelan@hrcc.on.ca

Eric Paul Winer

Dana-Farber Cancer Institute
44 Binney St
Room D1210
Boston, MA 02115-6084
USA
E-mail: ewiner@partners.org

Zee Wan Wong

Department of Medical Oncology
National Cancer Centre
11 Hospital Drive
Singapore
E-mail: dmowzw@nccs.com.sg

William Wood

Department of Surgery
Emory University Hospital
1364 Clifton Road NE B206
Atlanta, GA 30322-1059
USA
E-mail: William_wood@emory.org

Lilly Yang

Department of Surgery and Winship Cancer Institute
Emory University School of Medicine
1365 C Clifton Road, B4100
Atlanta, GA 30322
USA
E-mail: lyang02@emory.edu

Thomas Yang

Department of Radiation Oncology
UT MD Anderson Cancer Center
1515 Holcombe Boulevard
Houston, TX 77030
USA

Dihua Yu

Department of Surgical Oncology
Department of Molecular and Cellular Oncology
Division of Surgery
Box 107
The University of Texas MD Anderson Cancer Center
1515 Holcombe Boulevard
Houston, TX 77030
USA
E-mail: dyu@mdanderson.org

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