MEDITERRANEAN SCHOOL OF ONCOLOGY

CINBO
Consorzio Interuniversitario Nazionale
per la Bio-Oncologia

Director
Clara Natoli

Consorzio Interuniversitario Nazionale
per la Bio-Oncologia

is pleased to present

ADVANCES IN TARGETING CANCER PATHWAYS

by Cinbo delegates

April 8, 2016

Rome, Italy
Domus Sessoriana
P.zza Santa Croce in Gerusalemme n. 10

The new era of personalized oncology

Prof. Silverio Tomao

Università Sapienza di Roma

Polo Pontino

illumina

"And that's why we're here today. Because something called precision medicine … gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen."

President Barack Obama

January 30, 2015

Personalized Medicine

The National Cancer Institute (NCI) has defined personalized medicine …"as a form of medicine that uses information about a person's genes, proteins and environment to prevent, diagnose and treat disease"

American Cancer Society 2014
Li T J Clin Oncol 2013
National Cancer Institute. Dictionary of cancer terms
Grullich C Onkologie 2012

Personalized Medicine

Personalized medicine has changed the paradigms in oncology, because it is now based on understanding molecular carcinogenesis, pharmacogenomics, and individual genetic differences that determine the response to chemotherapeutics

American Cancer Society 2014
Li T J Clin Oncol 2013
National Cancer Institute. Dictionary of cancer terms
Grullich C Onkologie 2012

Personalized Oncology

Personalized oncology includes the concept that each individual solid tumor and hematologic malignancy in each person is unique in cause, rate of progression and responsiveness to surgery, chemotherapy and radiation therapy

Genomic and proteomic technologies have made it possible to subclassify diseases individually using the knowledge of the molecular basis of cancer

Ross JS Biomarkers Med 2011
Ginsburg GS Trends Biotechnol 2001

Personalized Oncology

Personalized oncology goals are the following:

- select optimal drug targets
- select optimal drug dosage
- predict which individuals will respond to specific drugs at high rates and who will be less likely to suffer toxic effects
- select and monitor patients for shorter less expensive advanced clinical trials
- reduce the overall cost of drug development
- Increase value and provide more effective healthcare for patients

Madhu K Metabolism 2013

Personalized Oncology

Expanding knowledge of tumour biology and tumour–host interactions has moved the field of cancer therapeutics in several new directions:

• Development of targeted therapies designed to interrupt molecular pathways known to be critical for cell growth and survival

Schilsky RL Nature Reviews 2010

Personalized Oncology

- Molecular profiling of tumours to better assess prognosis and likelihood of benefit from treatment

Schilsky RL Nature Reviews 2010

Personalized Oncology

- Development of single-gene or multigene expression signatures of response or resistance to particular drug treatments

Schilsky RL Nature Reviews 2010

Personalized Oncology

- Development of vaccine therapies and other immunological approaches that are highly specific to each individual tumour

Schilsky RL Nature Reviews 2010

Personalized Oncology

Even though this transition from empiric to mechanism-based, molecular biomarker-driven therapeutic decision process is still evolving, new classes of drugs and companion diagnostics are already beginning to emerge

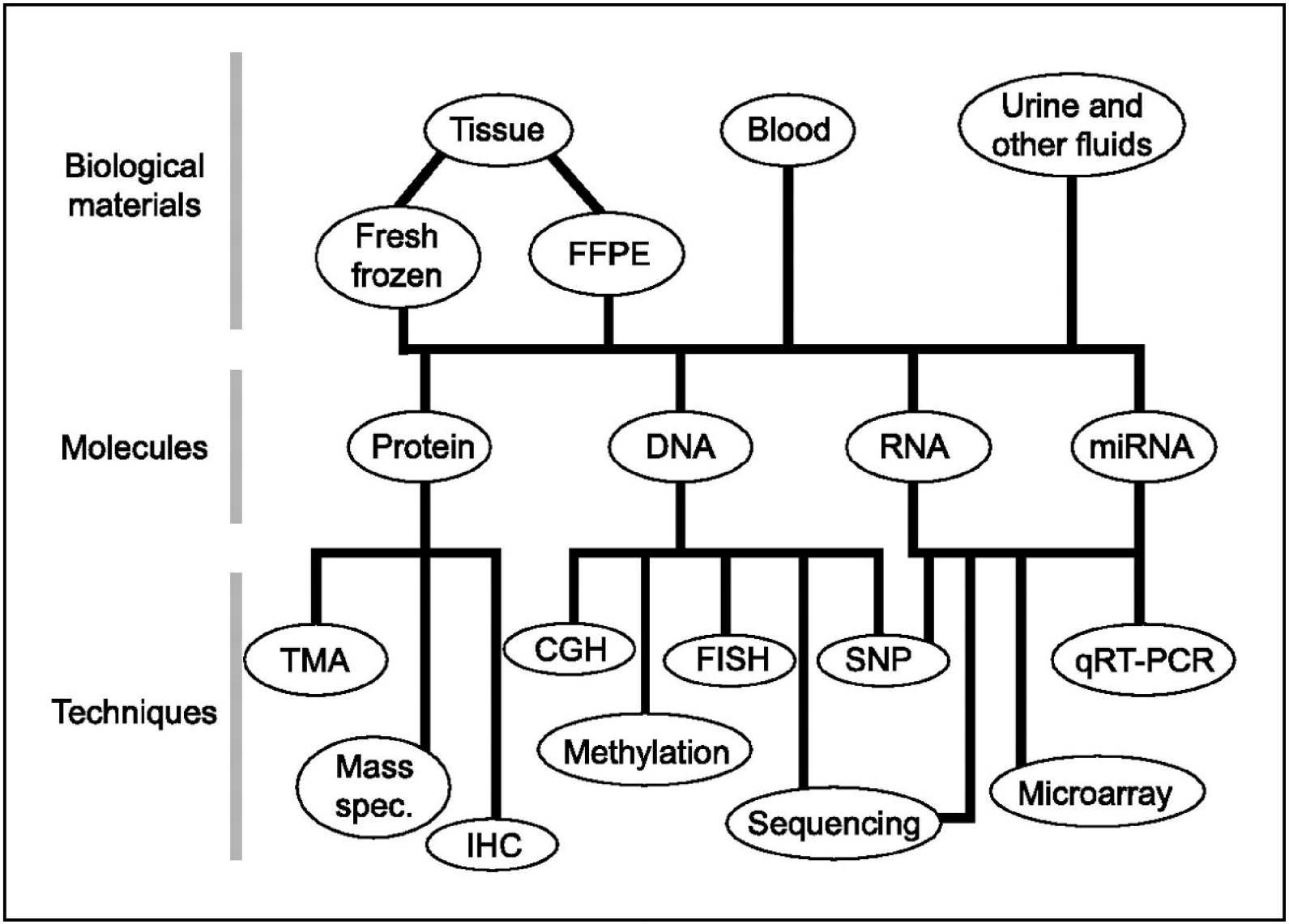
These are changing the landscape for the management of many advanced-stage cancers

Benefits of PM for the pharmaceutical industry

- Reduce time and cost of lead discovery
- Development of targeted therapies for specific cancer subgroups
- Improved patient selection for clinical trials
- Reduced timelines and costs of clinical trials
- Novel applications for old drugs

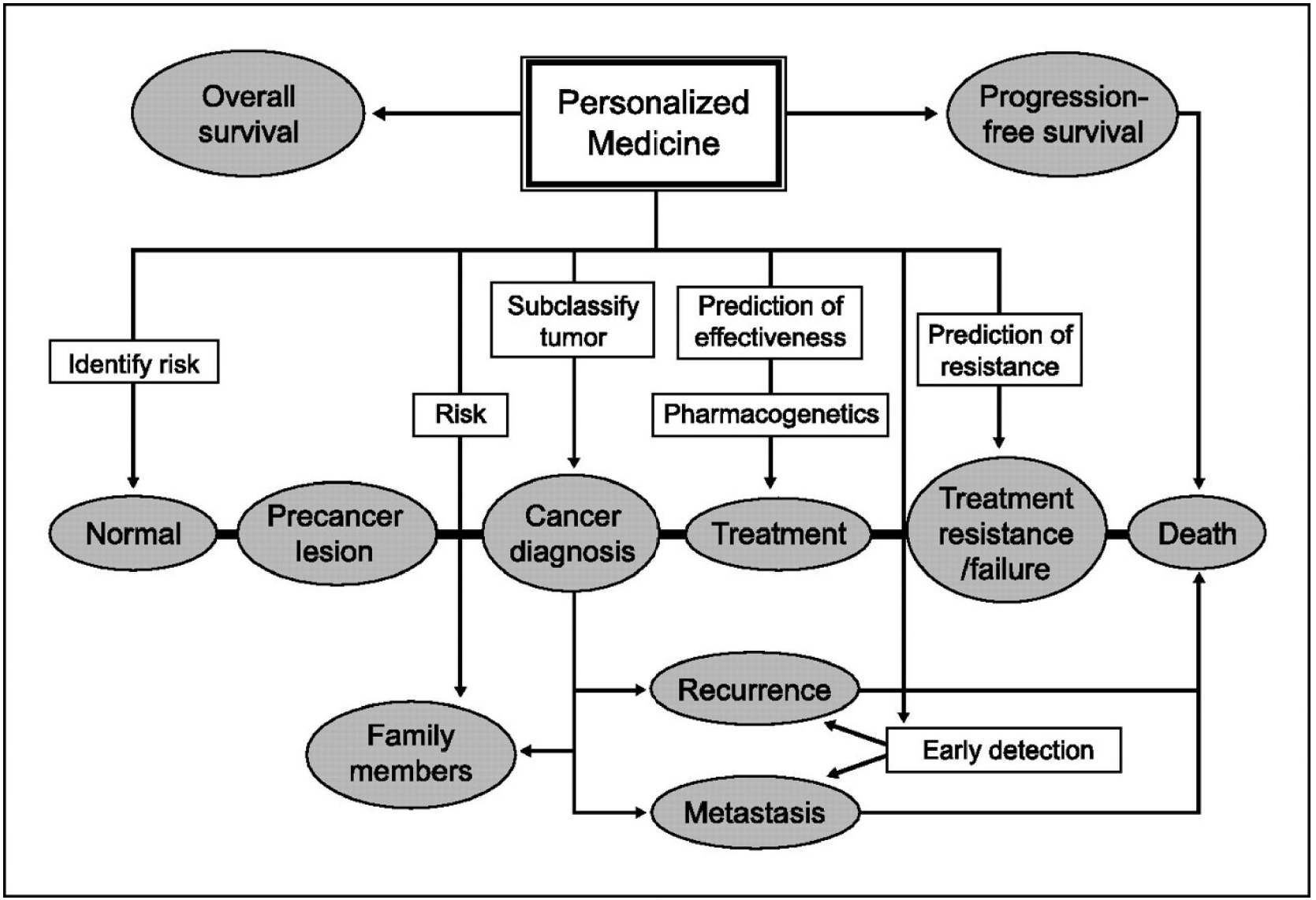
Maria Diamandis et al. Mol Cancer Res 2010;8:1175-1187

A schematic representing different approaches available for PM molecular testing



Maria Diamandis et al. Mol Cancer Res 2010;8:1175-1187

A schematic representing the future use of PM through the course of a cancer patients' disease



Maria Diamandis et al. Mol Cancer Res 2010;8:1175-1187

A New Taxonomy of Cancer

From organs to molecules

→Genomics and the Future of Cancer Treatment

According to the President of the Dana Farber Cancer Institute, we may soon look at the concept of "organ-based" cancer types as ancient history.

- For more than a century, cancers have been **classified by the organ or tissue** – *with therapies geared to those specific areas*
- As more is learned about the basic biological processes in cancers, a new perspective has emerged
- The shift from an organ-focused to a ***gene-focused approach*** to cancer is already having a profound effect on the way cancer is treated

Diagnostic biomarkers

Also called predictive biomarkers (targets for diagnostic intervention) are identified by characterizing key mutations and molecular pathways involved in tumor development and proliferation

These predictive biomarkers help optimize therapy decisions by providing information about the likelihood of a response to a chemotherapeutic intervention

Nalejska E Mol Diagn Ther 2014

Prognostic biomarkers

Identify somatic germline mutations, changes in DNA methylation, elevated levels of microRNA and circulating tumor cells in blood

Nalejska E Mol Diagn Ther 2014

Treatment and prevention biomarkers

Treatment and prevention biomarkers require more accurate molecular analysis
to guide individual therapy by identifying patients with different outcome risks (such as recurrence of the disease)

Nalejska E Mol Diagn Ther 2014

Treatment and prevention biomarkers

Information provided concurrently by predictive (diagnostic) and prognostic biomarkers makes possible quicker diagnoses and more accurate treatment choices

Predictive biomarkers using molecular diagnostics are currently in use in clinical practice of personalized oncology for the treatment of following five diseases: chronic myeloid leukemia, colon, breast and lung cancer and melanoma

Nalejska E Mol Diagn Ther 2014

Treatment and prevention biomarkers

Examples of these molecularly targeted therapies are: tyrosine kinase inhibitors in chronic myeloid leukemia (CLM) and gastrointestinal tumors; anaplastic lymphoma kinase (ALK) inhibitors in lung cancer with EML4-Alk fusion; HER2/neu blockage in HER2/neu-positive breast cancer; and epidermal growth factor receptors (EGFR) inhibition in EGFRmutated lung cancer

Nalejska E Mol Diagn Ther 2014

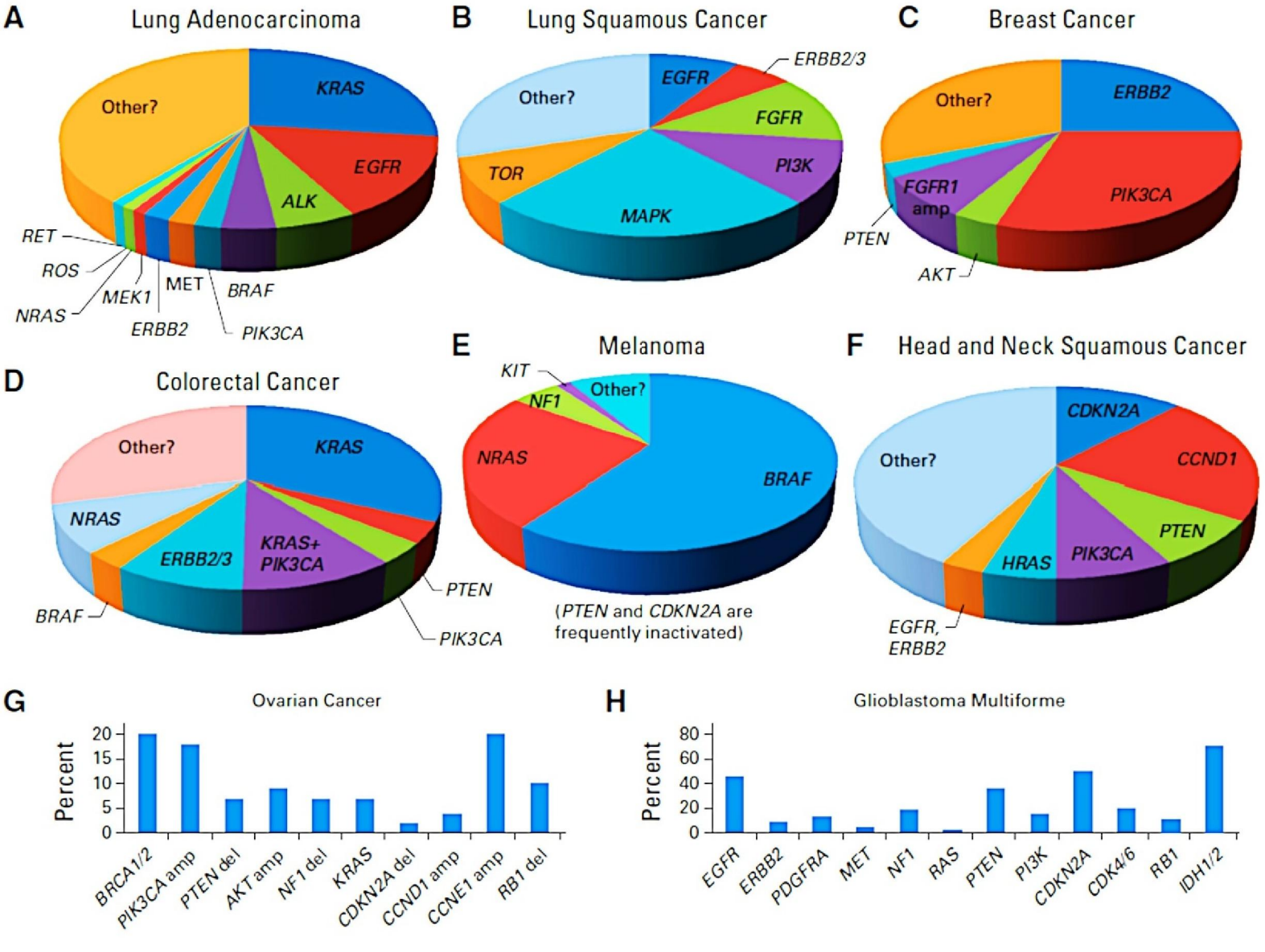
Biological roles of oncological predictive biomarkers

Table 1 | **Biomarkers of established or potential clinical utility to guide therapy**

Tumour type	Biomarker	Potential clinical use
Breast	Steroid hormone receptors	Select hormone therapy
Breast	HER2	Select trastuzumab use
Breast	Oncotype Dx gene profile	Assess prognosis; select chemotherapy
Colon	KRAS mutation status	Guide EGFR-specific antibody use
Colon	Microsatellite instability	Assess prognosis or utility of 5-fluoruracil adjuvant treatment
Non-small cell lung	EGFR mutation	Guide selection or use of EGFR tyrosine kinase inhibitors
Non-small cell lung	ERCC1	Select platinum-based chemotherapy
Glioblastoma	MGMT methylation	Guide temozolomide use
Melanoma	BRAF V600E mutation	Select therapy

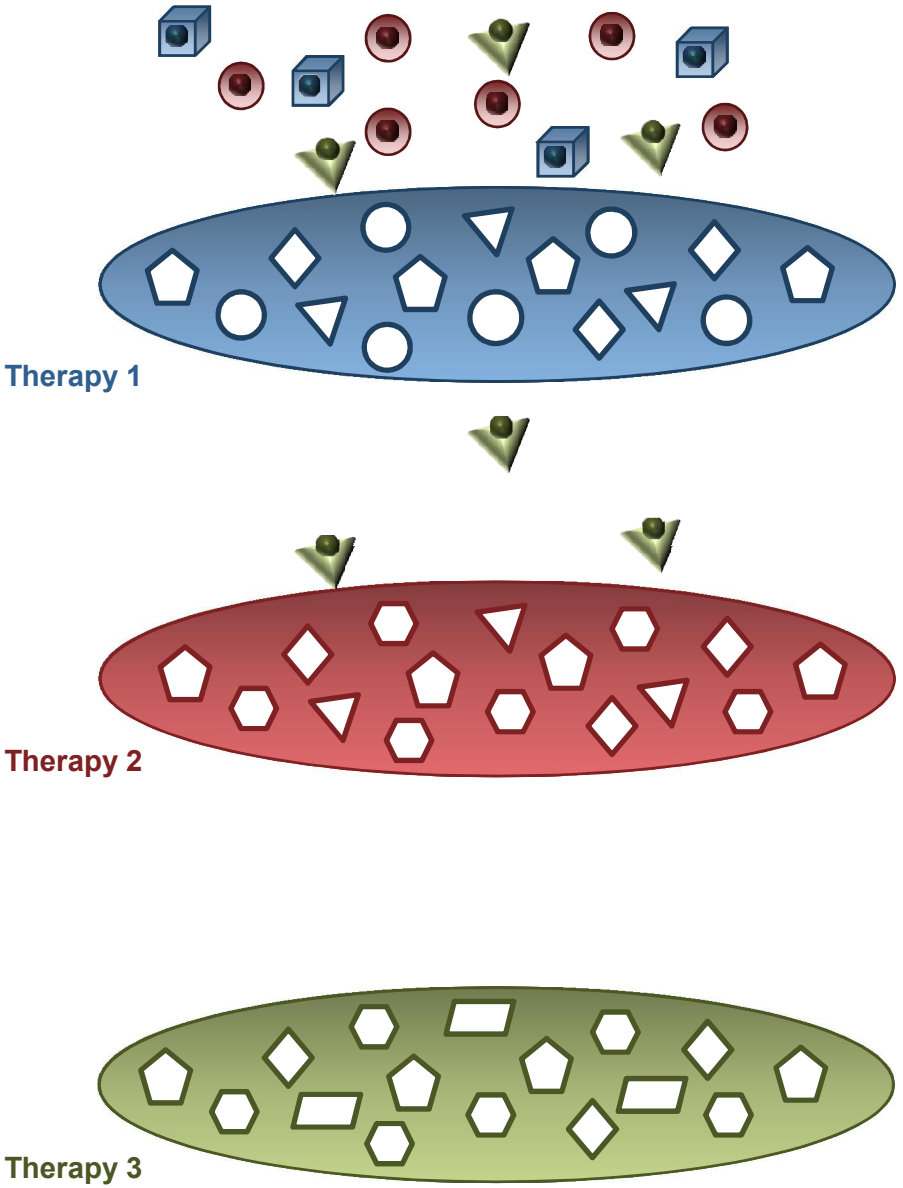
A New Taxonomy of Cancer

From organs to molecules



Garraway LA. Genomics-driven oncology: framework for an emerging paradigm. Journal of Clinical Oncology, 31(15), 1806-1814 (2013).

Cancer Is A Heterogeneous Disease



Need For Combination Therapies

A tumor consists of…

- **genetically distinct subpopulations** of cancer cells, each with its own **characteristic sensitivity profile** to a given therapy

Each cancer therapy can be viewed as…

- a **filter** that removes a subpopulation of cancer cells that are sensitive to this treatment

Combination therapy…

- for management of cancer as a ***chronic disease***

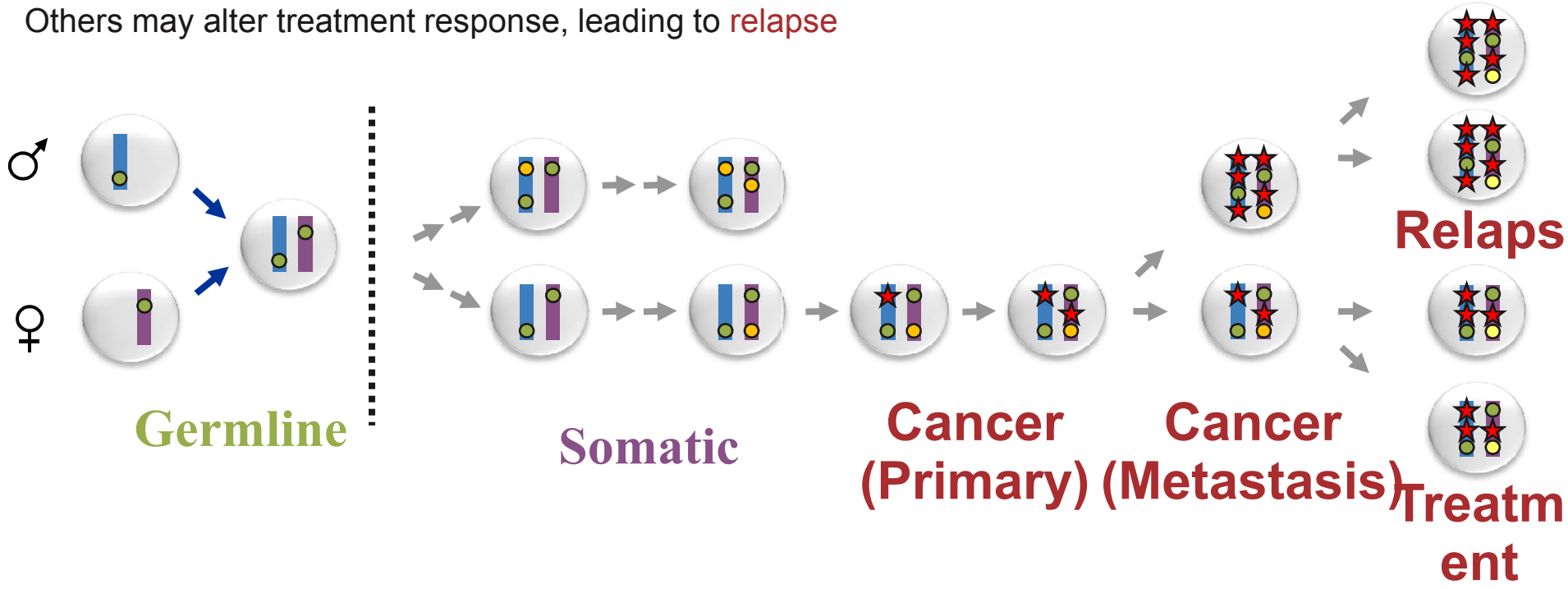
Adapated from Luo J, Solimini NL, Elledge SJ. Principles of cancer therapy: oncogene and non-oncogene addiction. *Cell*, 136(5), 823-837 (2009).

Cancer Genomes Are Dynamic

- WGS is a snapshot
- Certain mutations reflect paternal and/or maternal germline variation
- Additional somatic mutations accumulate through life
- "Driver" mutations cause cancer, "*passenger" mutations* are carried along
- Additional drivers evolve and diversify the cancer
- Some alter aggressiveness…
- …which may be treatable
- Others may alter treatment response, leading to relapse

Cancer genomes are not static.

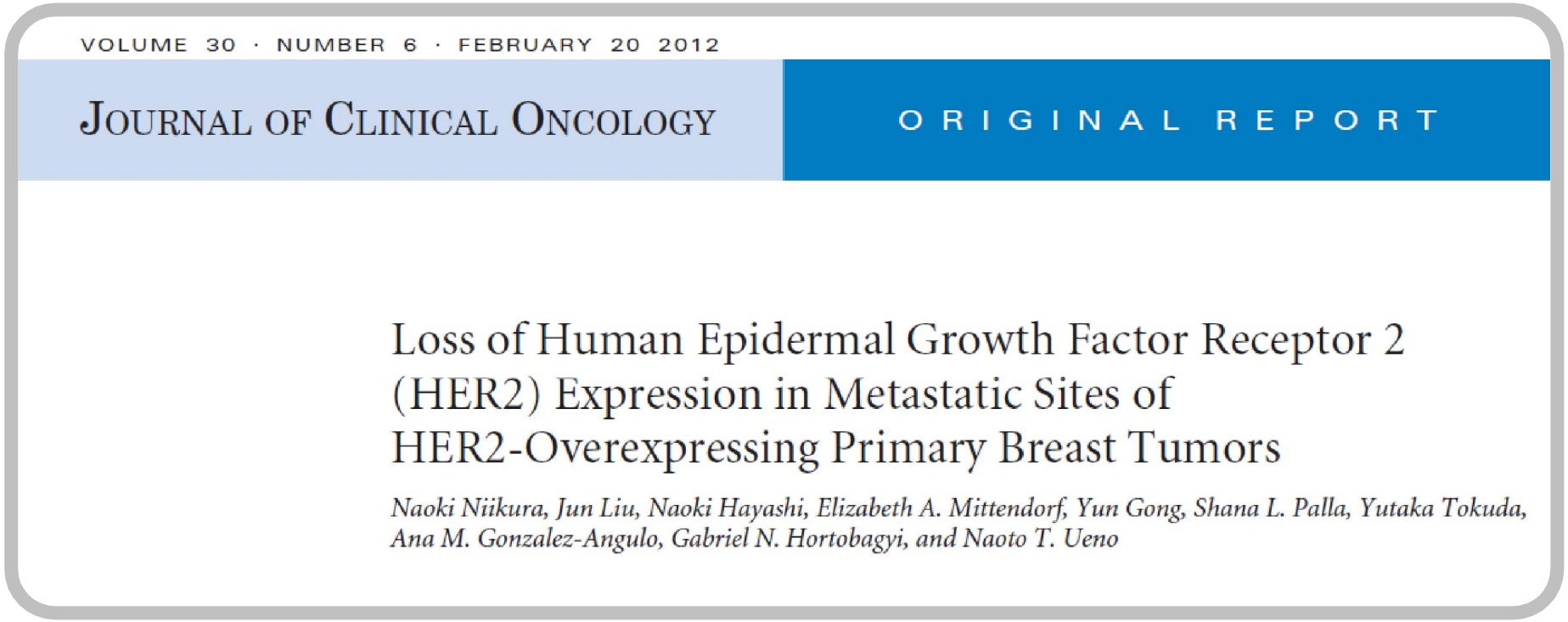
In cancer, one snapshot is not enough.



illumina

Evolution of Cancer Genomes

Primary vs. metastatic tumors

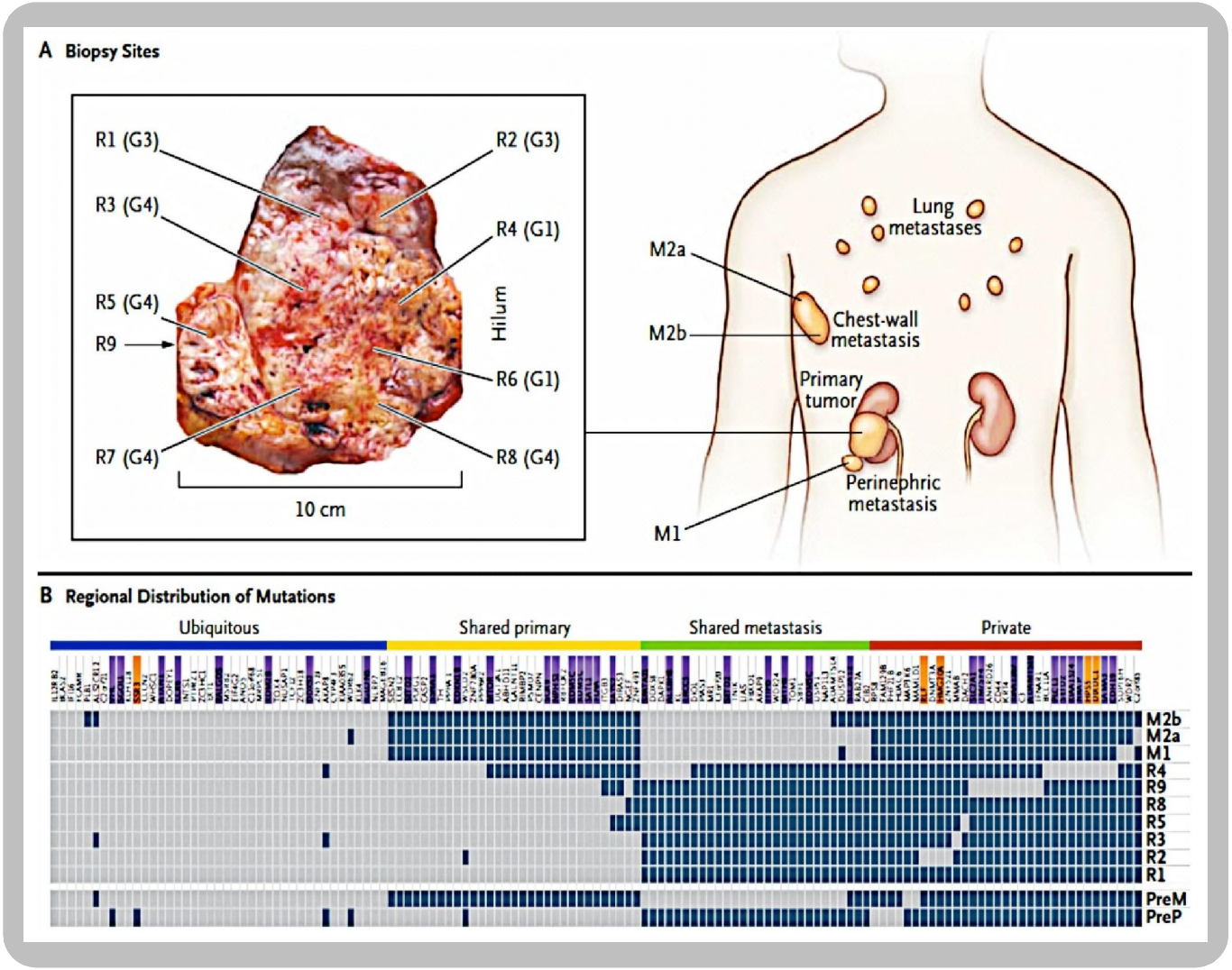


24% of patients with *HER2*-positive primary breast tumors had *HER2*-negative metastatic tumors

Niikura N, Liu J, Hayashi N *et al.* Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 30(6), 593-599 (2012).

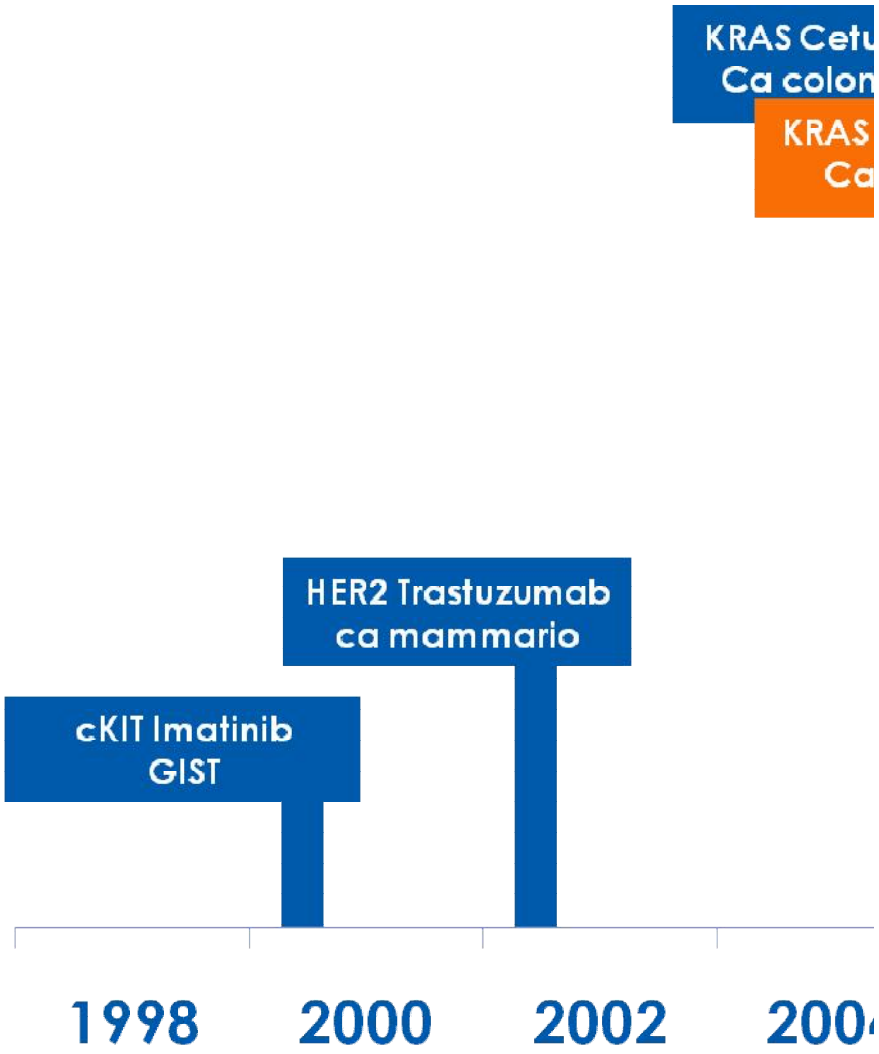
Intratumoral & Intermetastatic Clonal Heterogeneity

Heterogeneity within single patient



Gerlinger M, Rowan AJ, Horswell S *et al.* Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *The New England Journal of Medicine*, 366(10), 883-892 (2012).

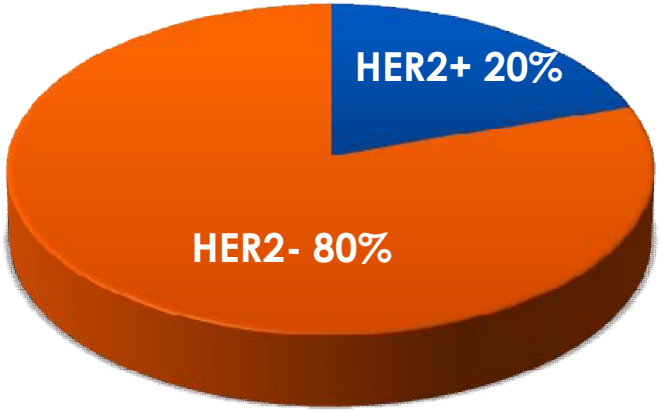
Terapia dei tumori solidi “personalizzata” biomarker-dipendente



Terapia dei tumori solidi “personalizzata” biomarker-dipendente

Agente	Biomarker	Tipo di tumore	Registrazione
Imatinib	c-Kit mutato	GIST	Metastatico, adiuvante alto rischio
Trastuzumab	HER2 iperespressione/ amplificazione	Carcinoma mammario	Adiuvante/ metatastico HER2+
		Carcinoma dello stomaco	Metastatico HER2+
Cetuximab	KRAS wild type	Carcinoma del colon-retto	Metastatico in combinazione con chemioterapia KRASwt
Panitumumab	KRAS wild type	Carcinoma del colon-retto	Metastatico pretrattato monoterapia KRASwt
Gefitinib	EGFR mutato	Adenocarcinoma del polmone	IIIIB-IV EGFRm
Erlotinib	EGFR mutato	Adenocarcinoma del polmone	IIIB-IV EGFRm; modifica registrazione EMA
Crizotinib	EML4-ALK fusione	NSCLC	IIII-IV; registrazione FDA; in valutazione EMA
Vemurafenib	BRAF mutato	Melanoma	Metastatico/non-resecabile; registrazione FDA; in valutazione EMA

Terapia dei tumori solidi “personalizzata” biomarker-dipendente – HER2 mammella



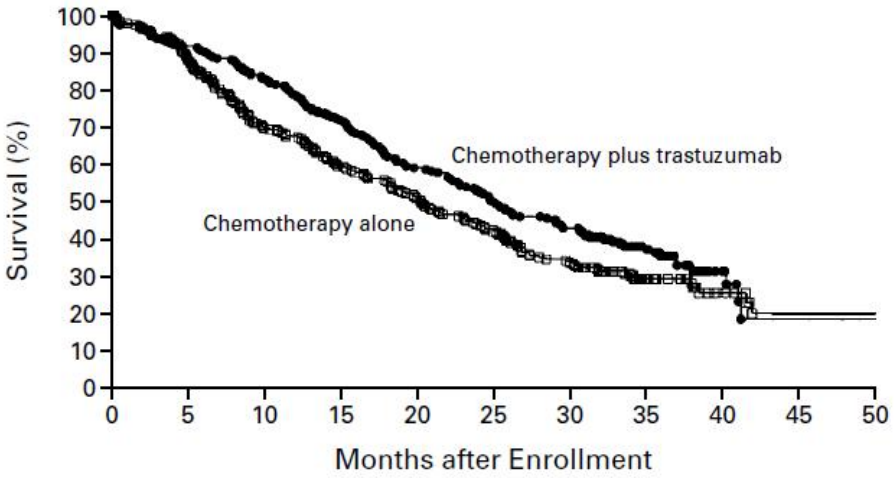
The New England Journal of Medicine

Copyright © 2001 by the Massachusetts Medical Society

VOLUME 344 · MARCH 15, 2001 · NUMBER 11

USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*



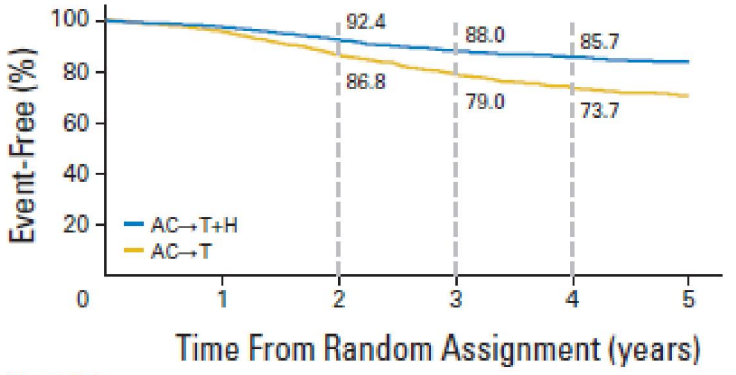
VOLUME 29 · NUMBER 25 · SEPTEMBER 1 2011

JOURNAL OF CLINICAL ONCOLOGY

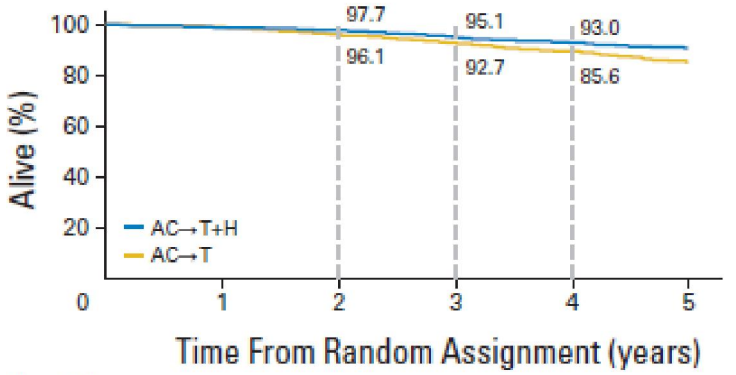
ORIGINAL REPORT

Four-Year Follow-Up of Trastuzumab Plus Adjuvant Chemotherapy for Operable Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Joint Analysis of Data From NCCTG N9831 and NSABP B-31

Edith A. Perez, Edward H. Romond, Vera J. Suman, Jong-Hyeon Jeong, Nancy E. Davidson, Charles E. Geyer Jr, Silvana Martino, Eleftherios P. Mamounas, Peter A. Kaufman, and Norman Wolmark

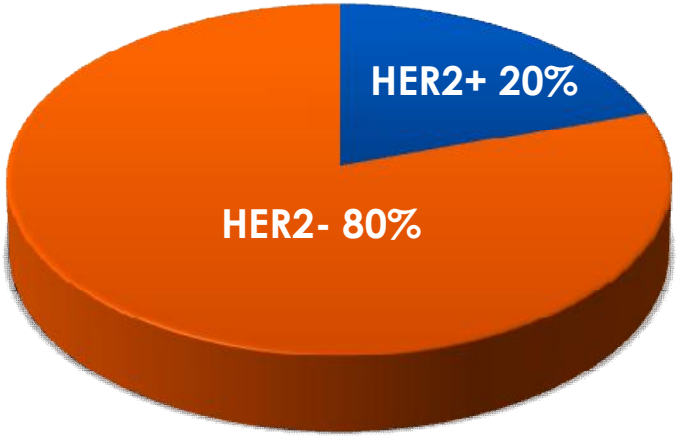


No. at risk					
AC→T+H	1,952	1,756	1,300	891	495
AC→T	1,881	1,652	1,132	702	395



No. at risk					
AC→T+H	1,991	1,875	1,420	976	554
AC→T	1,960	1,816	1,375	886	503

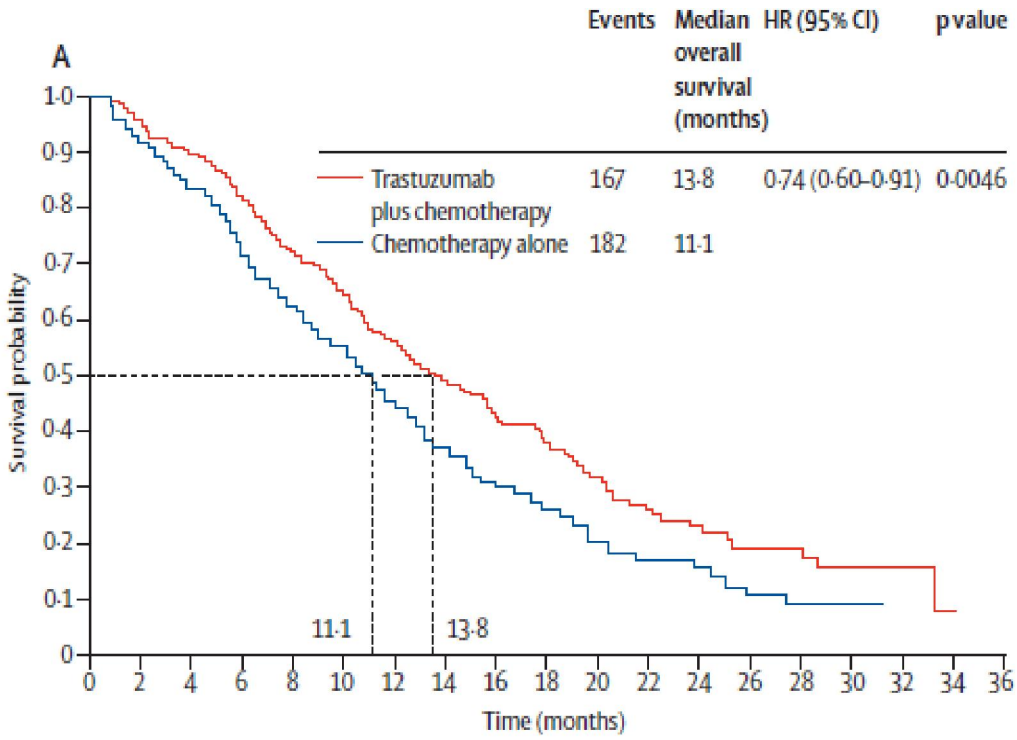
Terapia dei tumori solidi “personalizzata” biomarker-dipendente – HER2 stomaco



www.thelancet.com Vol 376 August 28, 2010

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

Yung-Jue Bang,* Eric Van Cutsem,* Andrea Feyereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro, Taroh Satoh, Giuseppe Aprile, Evgeny Kulikov, Julie Hill, Michaela Lehle, Josef Rüschoff, Yoon-Koo Kang, for the ToGA Trial Investigators†



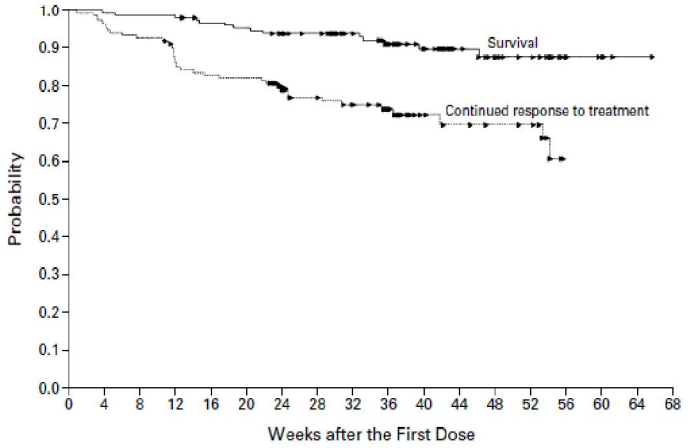
Terapia dei tumori solidi “personalizzata” biomarker-dipendente – cKit GIST

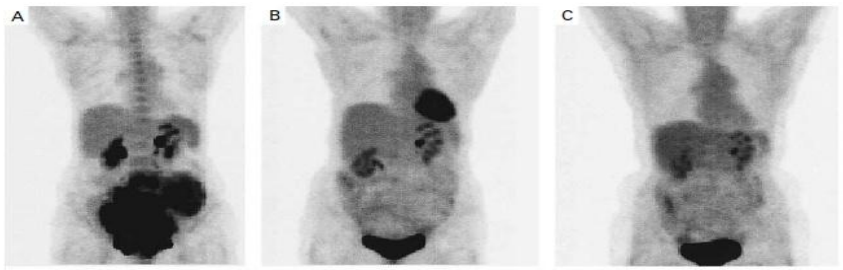
N Engl J Med, Vol. 347, No. 7 · August 15, 2002 · www.nejm.org

The New England Journal of Medicine

EFFICACY AND SAFETY OF IMATINIB MESYLATE IN ADVANCED GASTROINTESTINAL STROMAL TUMORS

GEORGE D. DEMETRI, M.D., MARGARET VON MEHREN, M.D., CHARLES D. BLANKE, M.D., ANNICK D. VAN DEN ABBEELE, M.D., BURTON EISENBERG, M.D., PETER J. ROBERTS, M.D., MICHAEL C. HEINRICH, M.D., DAVID A. TUVESON, M.D., PH.D., SAMUEL SINGER, M.D., MILOS JANICEK, M.D., PH.D., JONATHAN A. FLETCHER, M.D., STUART G. SILVERMAN, M.D., SANDRA L. SILBERMAN, M.D., PH.D., RENAUD CAPDEVILLE, M.D., BEATE KIESE, M.SC., BIN PENG, M.D., PH.D., SASA DIMITRIJEVIC, PH.D., BRIAN J. DRUKER, M.D., CHRISTOPHER CORLESS, M.D., CHRISTOPHER D.M. FLETCHER, M.D., AND HEIKKI JOENSUU, M.D.

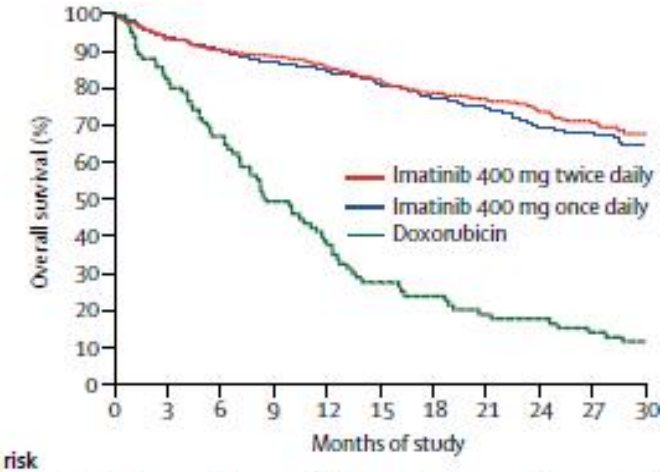




www.thelancet.com Vol 364 September 25, 2004

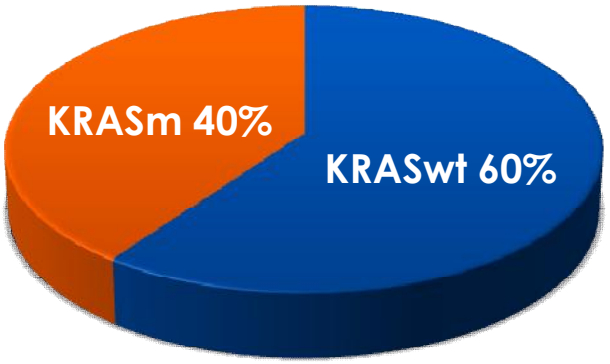
Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial

*Jaap Verweij, Paolo G Casali, John Zalcberg, Axel LeCesne, Peter Reichardt, Jean-Yves Blay, Rolf Issels, Allan van Oosterom, Pancras C W Hogendoorn, Martine Van Glabbeke, Rossella Bertulli, Ian Judson, for the EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group**



Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Terapia dei tumori solidi “personalizzata” biomarker-dipendente – KRAS colon-retto

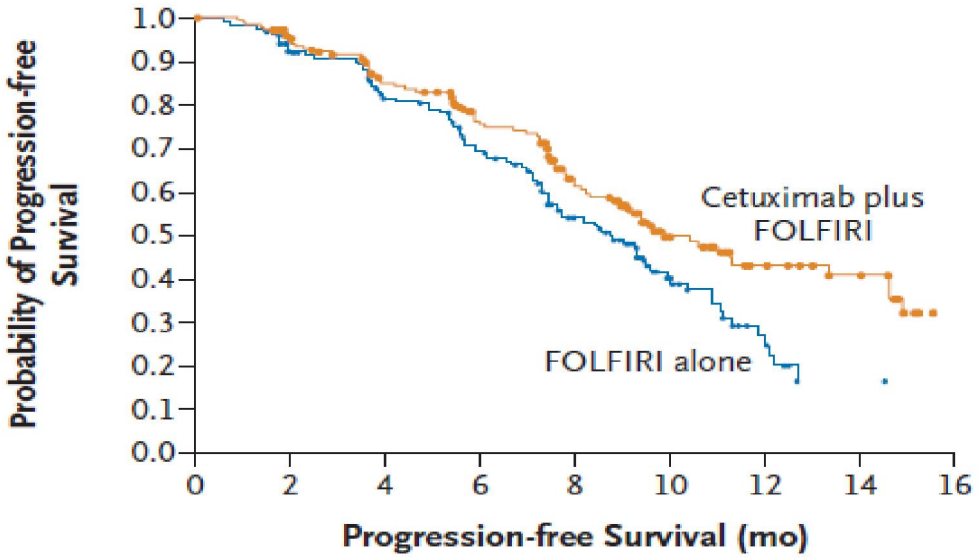


N ENGL J MED 360;14 NEJM.ORG APRIL 2, 2009

ORIGINAL ARTICLE

Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer

Eric Van Cutsem, M.D., Ph.D., Claus-Henning Köhne, M.D., Erika Hitre, M.D., Ph.D., Jerzy Zaluski, M.D., Chung-Rong Chang Chien, M.D., Anatoly Makhson, M.D., Ph.D., Geert D'Haens, M.D., Ph.D., Tamás Pintér, M.D., Robert Lim, M.B., Ch.B., György Bodoky, M.D., Ph.D., Jae Kyung Roh, M.D., Ph.D., Gunnar Folprecht, M.D., Paul Ruff, M.D., Christopher Stroh, Ph.D., Sabine Tejpar, M.D., Ph.D., Michael Schlichting, Dipl.-Stat., Johannes Nippgen, M.D., and Philippe Rougier, M.D., Ph.D.



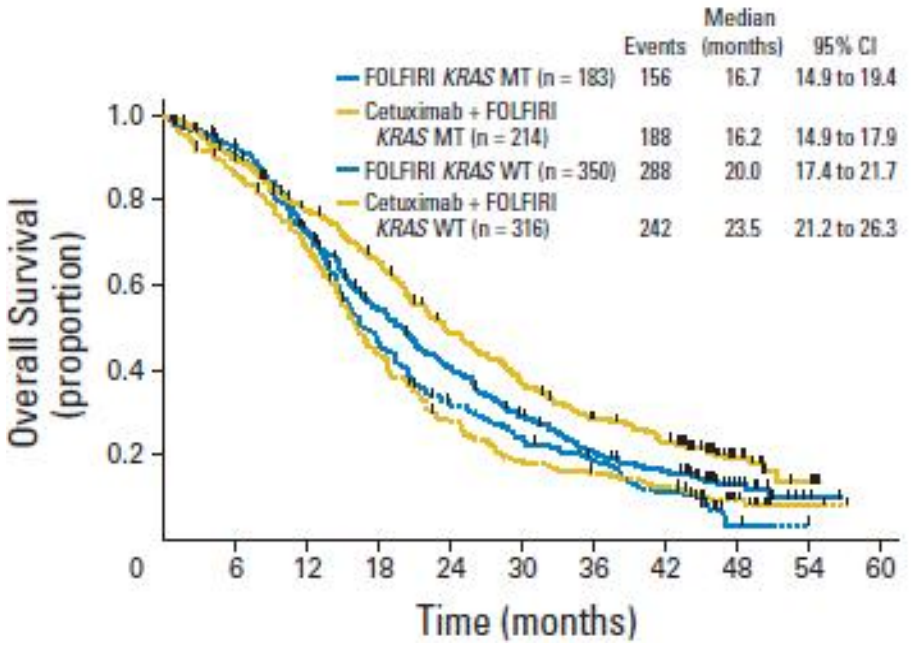
Published Ahead of Print on April 18, 2011 as 10.1200/JCO.2010.33.5091
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2010.33.5091

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

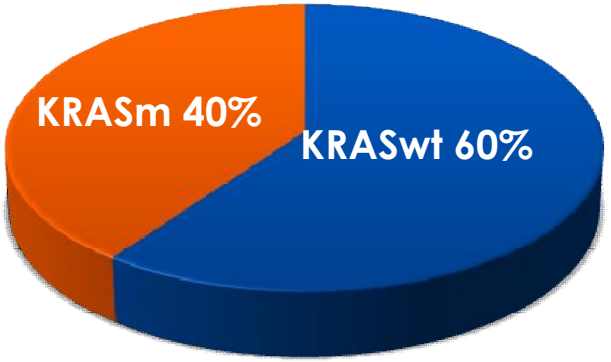
Cetuximab Plus Irinotecan, Fluorouracil, and Leucovorin As First-Line Treatment for Metastatic Colorectal Cancer: Updated Analysis of Overall Survival According to Tumor *KRAS* and *BRAF* Mutation Status

From the University Hospital Gasthuisberg, Leuven, Belgium; Klinikum Oldenburg, Oldenburg; University Hospital Carl Gustav Carus, Dresden; Merck KGaA, Darmstadt,

Eric Van Cutsem, Claus-Henning Köhne, István Láng, Gunnar Folprecht, Marek P. Nowacki, Stefano Cascinu, Igor Shchepotin, Joan Maurel, David Cunningham, Sabine Tejpar, Michael Schlichting, Angela Zubel, Ilhan Celik, Philippe Rougier, and Fortunato Ciardiello



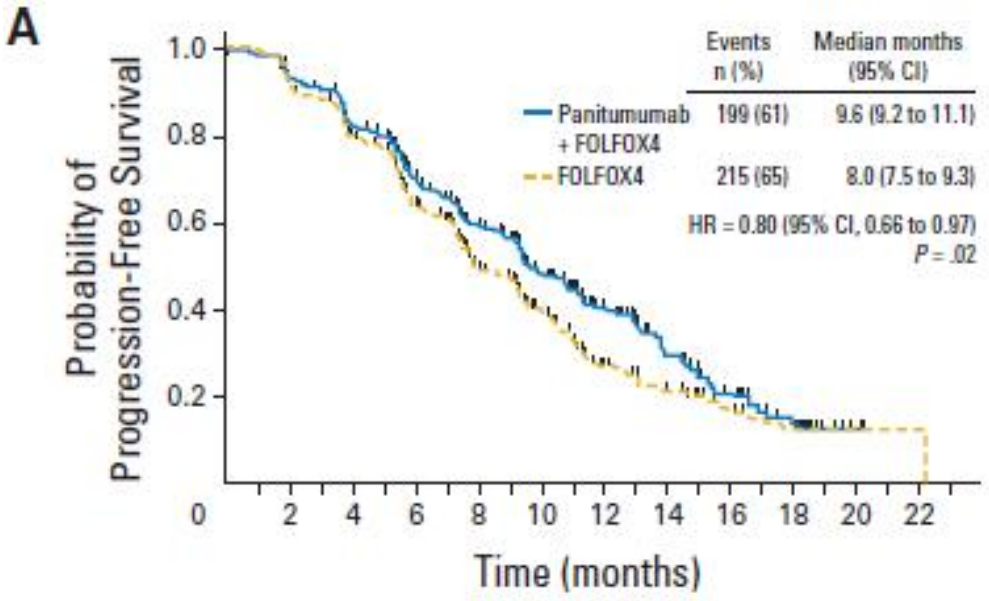
Terapia dei tumori solidi “personalizzata” biomarker-dipendente – KRAS colon-retto

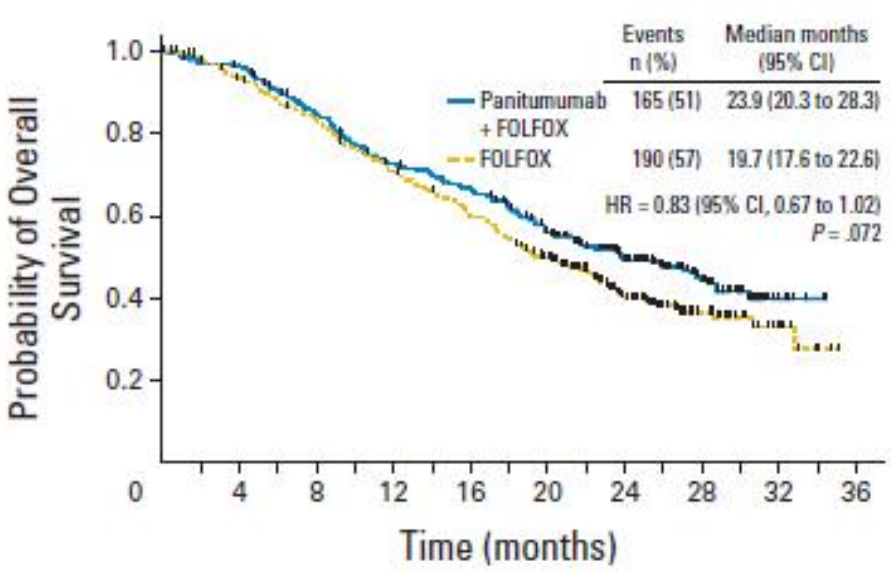


VOLUME 28 · NUMBER 31 · NOVEMBER 1 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

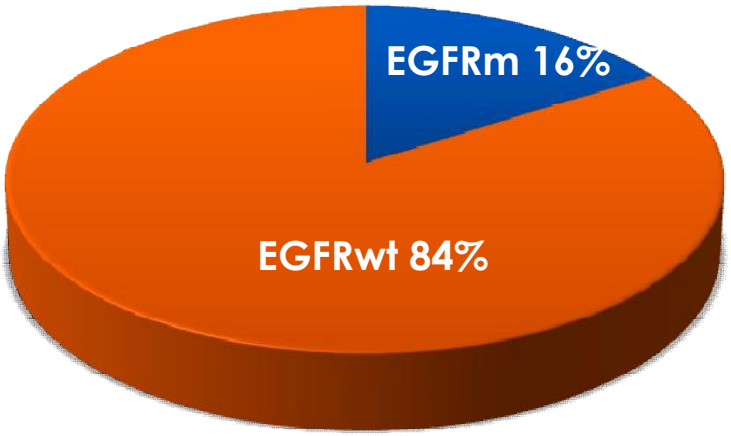
Randomized, Phase III Trial of Panitumumab With Infusional Fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX4) Versus FOLFOX4 Alone As First-Line Treatment in Patients With Previously Untreated Metastatic Colorectal Cancer: The PRIME Study

Jean-Yves Douillard, Salvatore Siena, James Cassidy, Josep Tabernero, Ronald Burkes, Mario Barugel, Yves Humblet, György Bodoky, David Cunningham, Jacek Jassem, Fernando Rivera, Ilona Kocákova, Paul Ruff, Maria Blasińska-Morawiec, Martin Šmakal, Jean-Luc Canon, Mark Rother, Kelly S. Oliner, Michael Wolf, and Jennifer Gansert





Terapia dei tumori solidi “personalizzata” biomarker-dipendente – EGFR polmone

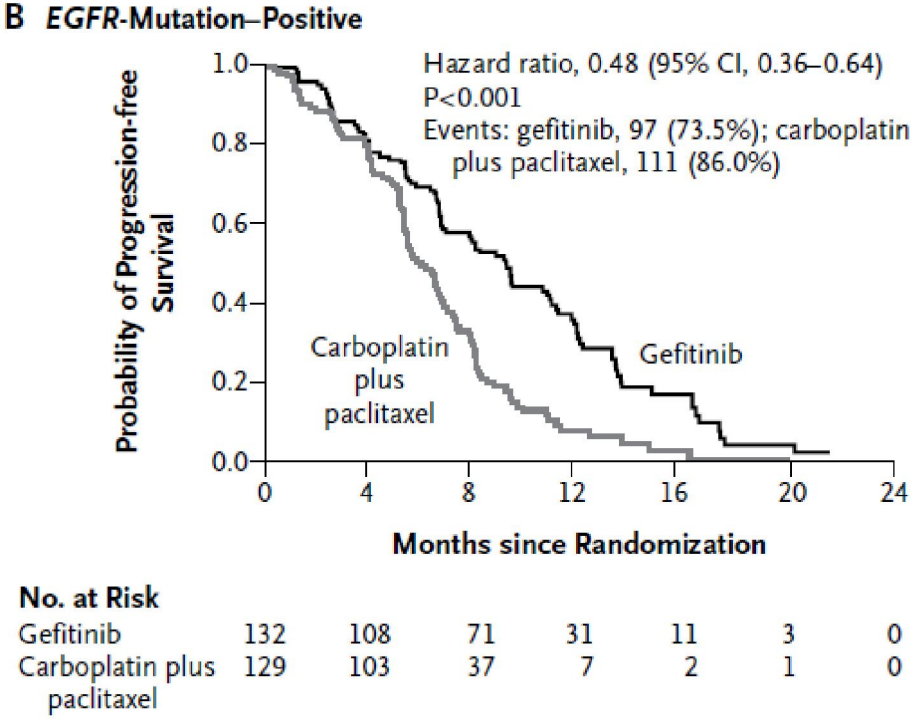


The NEW ENGLAND JOURNAL of MEDICINE

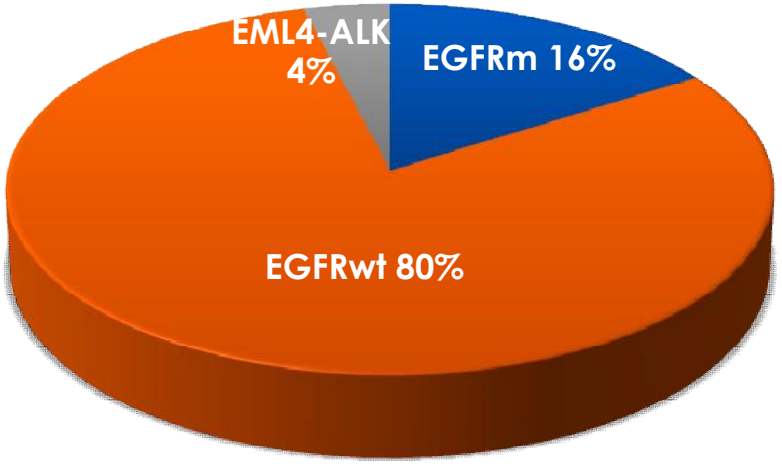
ESTABLISHED IN 1812 SEPTEMBER 3, 2009 VOL. 361 NO. 10

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Jin-Ji Yang, M.D., Busyamas Chewaskulyong, M.D., Haiyi Jiang, M.D., Emma L. Duffield, M.Sc., Claire L. Watkins, M.Sc., Alison A. Armour, F.R.C.R., and Masahiro Fukuoka, M.D., Ph.D.



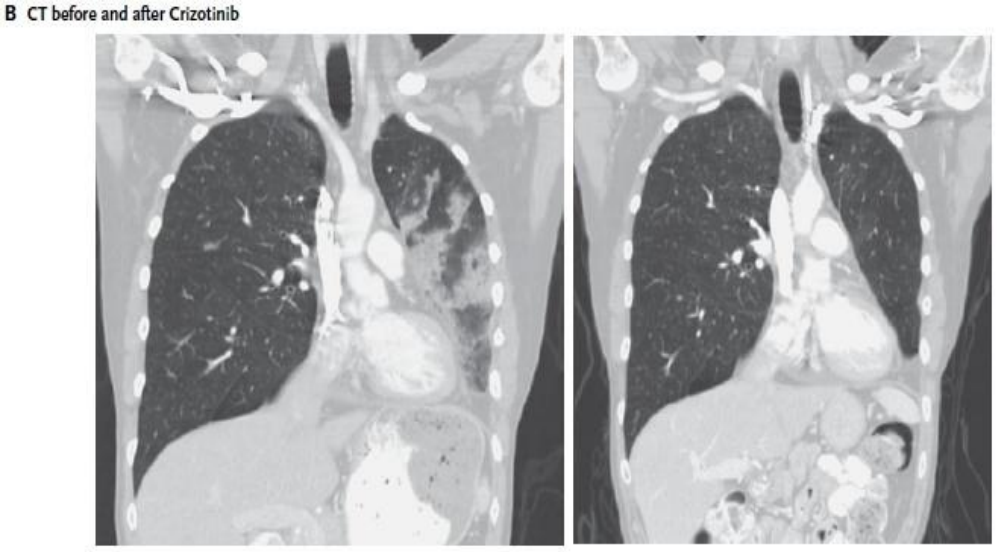
Terapia dei tumori solidi “personalizzata” biomarker-dipendente – EML4-ALK polmone

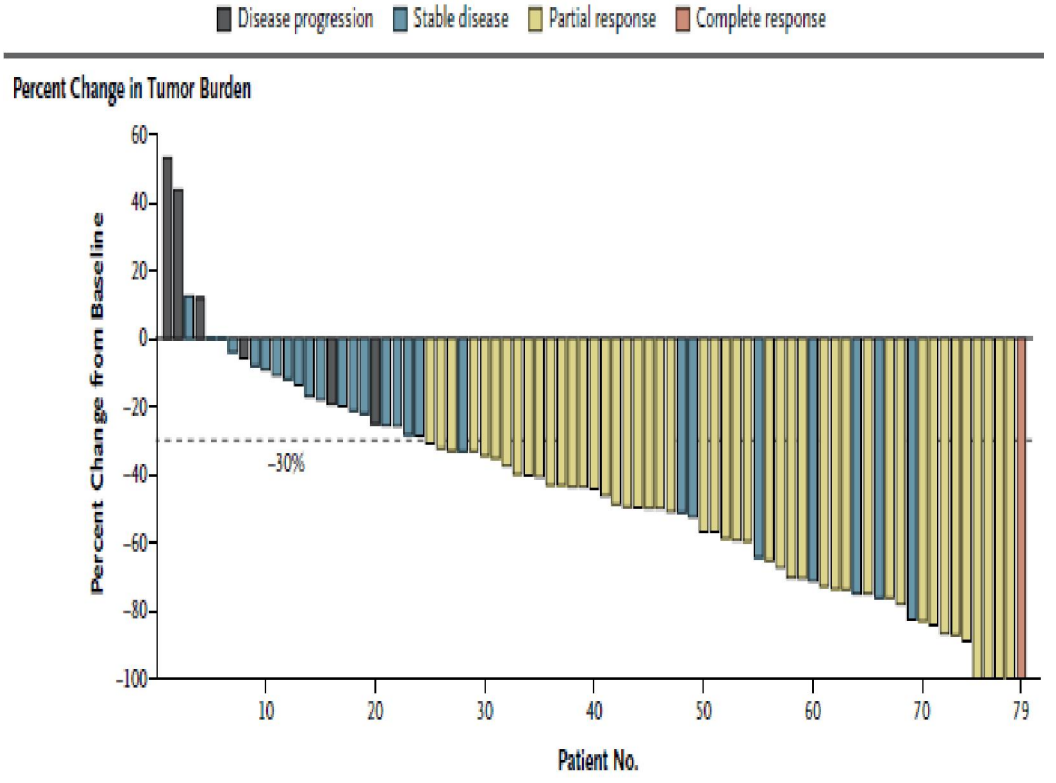


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

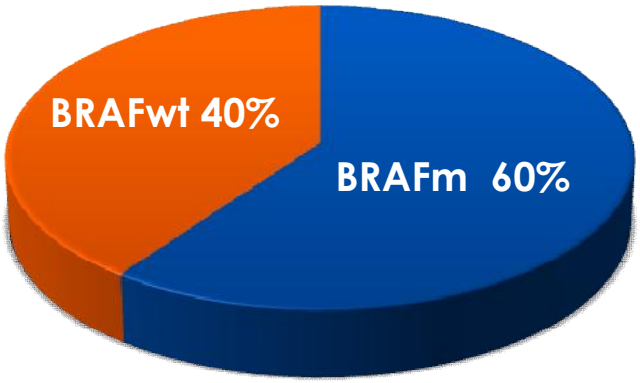
Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.





Terapia dei tumori solidi “personalizzata” biomarker-dipendente – BRAF melanoma

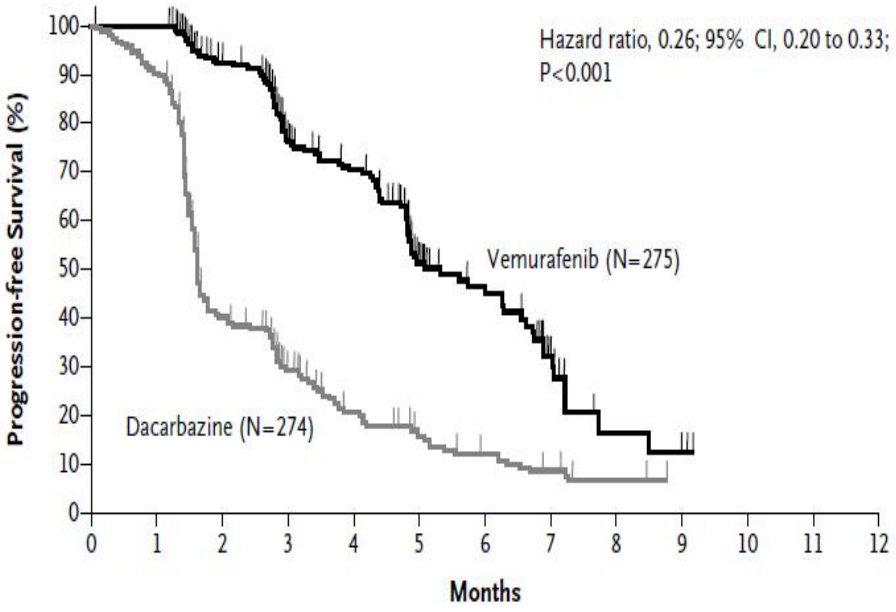


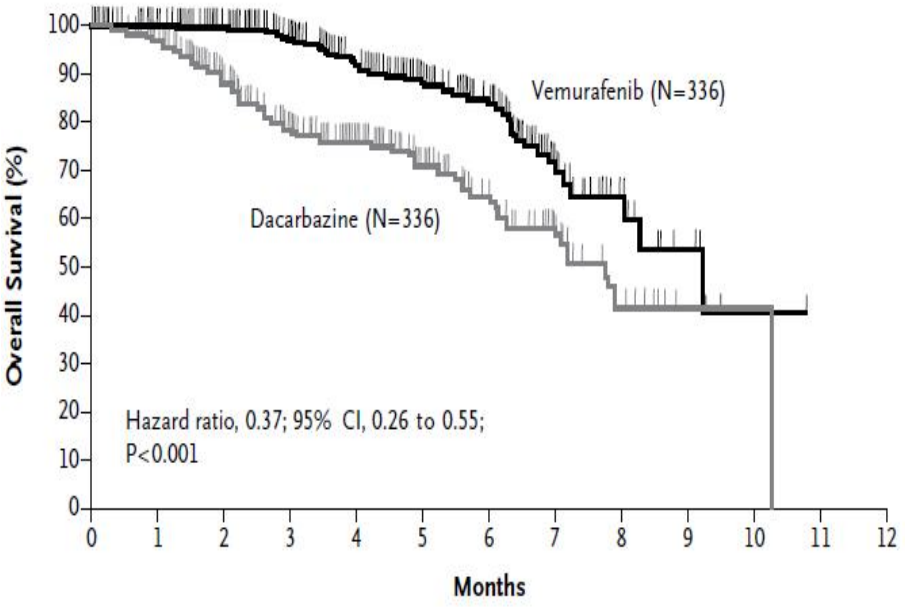
N Engl J Med 2011.

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*





Conclusions

In order for personalized medicine to continue to grow we need to stop searching for one drug to treat all patients with a specific indication

Hundreds of genomic alterations have been recorded for individual tumors, and our knowledge of these changes is growing

Personalized medicine needs to be integrated into clinical practice, to enhance diagnosis, prognosis, and prediction of disease. Molecular characteristics of tumors that have been identified need to be added to a patient's clinical characteristics

Conclusions

For cancer therapeutics this approach increases efficiency and productivity

Over the next ten years, it has been estimated personalized medicine will grow to 5%–10% of the entire pharmaceuticals market

Several companies are already establishing diagnostic divisions to identify new biomarkers and meet the related diagnostic needs in-house by combining drug development with the production of the related diagnostic test

Hoggart J Mol Diagn Ther 2011

Conclusions

A new molecular classification of many cancers has evolved based on chromosomal aberrations, gene mutations and signaling pathway activation that underlie biologically unique tumors that now need to be managed clinically in several different ways

Kalia M Metabolism 2013

Conclusions

The central goal of biomarker-based personalized cancer therapy is to make treatment decisions based on tumor genotypes and genetic profiles

Matching targeted therapies against specific genetic aberrations is an important step for personalized cancer therapy

Such an approach holds promise in ultimately improving measurable clinical outcomes:

response rates, survival and safety

Gandara DR Clin Lung Cancer 2012

Haber DA Cell 2011

Conclusions

As more epigenetic targets are identified, and with more than 800 anticancer therapeutics in clinical development, the obstacles to targeted therapy include the following:

- More drugs
- More diseases
- More use of placebo controls
- More use of randomized screening trials
- Longer time to reach end points
- More expensive documentation
- Multiple effective lines of therapy
- Greater regulatory complexity

Schilsky RL Nature Reviews 2010

Conclusions

Patients with cancer are not all the same and each person deserves nothing less than a personalized approach to their care

Schilsky RL Nature Reviews 2010

Thank You!