

## Title: Combinatorial Approaches against PI3 Kinase Pathway



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### **Speaker**



### **Masakazu Toi, M.D., Ph.D.**

Professor, Department of Surgery, Graduate School of  
Medicine Kyoto University, Japan

### **Chairman**

### **Jose Baselga, M.D., Ph.D.**

#### **EDUCATION:**

9/76-6/82 MD

Medicine

Universitat Autònoma de Barcelona,  
Spain

11/92 Ph.D.  
Cum Laude and  
Extraordinary Award

Universitat Autònoma de Barcelona,  
Spain

**FACULTY ACADEMIC APPOINTMENTS:**

- 7/94-6/96 Instructor, Medical, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, NY.
- 1/95-7/10 Professor, Medicine, Universitat Autònoma de Barcelona, Spain
- 2010- Professor, Medicine, Harvard Medical School, Boston, MA

**APPOINTMENTS AT HOSPITALS/AFFILIATED INSTITUTIONS:**

- 7/94-6/96 Clinical Assistant Physician, Breast/Gynecology Oncology Service, Department of Medicine
- 1/96-7/10 Chairman, Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain
- 7/10 - Physician, Medicine, Massachusetts General Hospital, Boston, MA.

**MAJOR ADMINISTRATIVE LEADERSHIP POSITIONS:**

- 1996-2010 Chairman, Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain
- 1996-2010 Director, Medical Oncology, Hematology and Radiation Oncology, Vall d'Hebron University Hospital, Barcelona, Spain
- 2007-2010 Director, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain
- 2010- Associate Director, MGH Cancer Center, Massachusetts General Hospital
- 2010- Division Chief, Division of Hematology/Oncology, Massachusetts General Hospital
- 2012- Associate Director Clinical Sciences, Dana Farber/Harvard Cancer Center (DF/HCC)

**PROFESSIONAL SOCIETIES:**

- 1990 American Society of Clinical Oncology
- 2004-2006 Member, Board of Directors.
- 2008-2011 Member, Trials in Progress Track, Scientific Program Committee
- 2010-2013 Member, Special Awards Selection Committee
- 1990 American Association for Cancer Research
- 2008-2011 Member, Board of Directors
- 2012-2013 Chairperson, 2013 Annual Meeting Program Committee
- 1996 Spanish Cooperative Breast Cancer Group (SOLTI)
- 2009- President
- 1996 European Society for Medical Oncology
- 2008-2009 President
- 2006-2012 Member, Board of Directors
- 2002 European Cancer Organization
- 2010-2011 Member, Board of Directors, Re-elected
- 2006 Ludwig Institute for Cancer Research
- 2006- Member, Scientific Advisory Committee
- 2008 American-Italian Cancer Foundation
- 2008- Member, Board of Directors
- 2008-2011 Member, Scientific Advisory Board
- 2010 Breast International Group
- 2010- Member, Board of Directors

**HONORS AND PRIZES:**

- 1992-1993 Young Investigator Award, American Society of Clinical Oncology (ASCO)
- 1999 Young Investigator Award, American Association for Cancer Research (AACR)
- 2003 Honorary Membership Award, The European Society for Therapeutic Radiology and Oncology (ESTRO)
- 2004 Waun Ki Hong Visiting Professorship, UTMD Anderson Cancer Center
- 2004 Distinguished Alumni Award, 29<sup>th</sup> Annual Alumni Society Meeting, Memorial Sloan-Kettering Cancer Center

2005	Annual Award, European Society of Medical Oncology (ESMO), Career Recognition Award
2005	Professional Excellence Award in Biomedicine Research, Barcelona College of Physicians
2006	City Award “The Key to the City of Barcelona”, Francisco Godia Foundation, Civic leadership in Barcelona
2006	Michael Clavel Lecture Award, 18 <sup>th</sup> EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Contributions in early drug development
2006	San Salvatore Prize 2006, San Salvatore Foundation, Achievements in breast cancer research
2007	AICF Prize For Scientific Excellence in Medicine, American Italian Cancer Foundation
2008	Civil Order of Health – Commander with Plaque, Ministry of Health, Government of Spain; Contribution to the advanced of biomedical science in Spain
2008	Rosenthal Family Foundation Award, American Association for Cancer Research, Academic career in translational oncology
2008	Rey Jaime I Award in Medical Research, King Jaime I Foundation, Achievements in biomedical research in cancer
2010	Bruce A. Chabner Chair in Hematology Oncology, Massachusetts General Hospital Cancer Center, Academic career achievements in Hematology/Oncology
2010	Bob Pinedo Cancer Care Prize, The Society for Translational Oncology (STO), Exceptional contribution to improved care for cancer patients
2010	Gold Medal, Queen Sofia Spanish Institute, Achievements in biomedical research in cancer
2011	Honorary Doctoral Degree, Valencia University, Career excellence and innovation in biomedical research in cancer
2012	Joseph B. Martin Award, Massachusetts General Hospital, Best clinical paper published by MGH Investigators in 2011

## **PUBLICATIONS:**

>280 publications in the peer reviewed journals.

Publications selected in the last 12 months:

1. Serra V, Scaltriti M, Prudkin L, Eichhorn PJ, Ibrahim YH, Chandarlapaty S, Markman B, Rodriguez O, Guzman M, Rodriguez S, Gili M, Russillo M, Parra JL, Singh S, Arribas J, Rosen N, Baselga J. PI3K inhibition results in enhanced HER signaling and acquired ERK dependency in HER2-overexpressing breast cancer. *Oncogene*. 2011 Jun 2;30(22):2547-57.
2. Lenihan D, Suter T, Brammer M, Neate C, Ross G, Baselga J. Pooled analysis of cardiac safety in patients with cancer treated with pertuzumab. *Ann Oncol*. 2012 Mar;23(3):791-800.

3. Bass AJ, Lawrence MS, Brace LE, Ramos AH, Drier Y, Cibulskis K, Sougnez C, Voet D, Saksena G, Sivachenko A, Jing R, Parkin M, Pugh T, Verhaak RG, Stransky N, Boutin AT, Barretina J, Solit DB, Vakiani E, Shao W, Mishina Y, Warmuth M, Jimenez J, Chiang DY, Signoretti S, Kaelin WG, Spardy N, Hahn WC, Hoshida Y, Ogino S, Depinho RA, Chin L, Garraway LA, Fuchs CS, Baselga J, Tabernero J, Gabriel S, Lander ES, Getz G, Meyerson M. Genomic sequencing of colorectal adenocarcinomas identifies a recurrent VT11A-TCF7L2 fusion. *Nat Genet.* 2011 Oct;43(10):964-8.
4. Semiglazov V, Eiermann W, Zambetti M, Manikhas A, Bozhok A, Lluch A, Tjulandin S, Sabadell MD, Caballero A, Valagussa P, Baselga J, Gianni L. Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study. *Eur J Surg Oncol.* 2011 Oct;37(10):856-63.
5. Serrano C, Cortés J, De Mattos-Arruda L, Bellet M, Gómez P, Saura C, Pérez J, Vidal M, Muñoz-Couselo E, Carreras MJ, Sánchez-Ollé G, Tabernero J, Baselga J, Di Cosimo S. Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. *Ann Oncol.* 2011 Aug 9.
6. Paz-Ares LG, Gomez-Roca C, Delord JP, Cervantes A, Markman B, Corral J, Soria JC, Berge Y, Roda D, Russell-Yarde F, Hollingsworth S, Baselga J, Umana P, Manenti L, Tabernero J. Phase I pharmacokinetic and pharmacodynamic dose-escalation study of RG7160 (GA201), the first glycoengineered monoclonal antibody against the epidermal growth factor receptor, in patients with advanced solid tumors. *J Clin Oncol* 2011 Oct 1;29(28):3783-90.
7. Atzori F, Tabernero J, Cervantes A, Prudkin L, Andreu J, Rodriguez-Braun E, Domingo A, Guijarro J, Gamez C, Rodon J, Di Cosimo S, Brown H, Clark J, Hardwick J, Beckman RA, Hanley W, Hsu K, Calvo E, Rosello S, Langdon RB, Baselga J. A Phase I, Pharmacokinetic and Pharmacodynamic Study of Dalotuzumab (MK-0646), an Anti-IGF-1R Monoclonal Antibody, in Patients with Advanced Solid Tumors. *Clin Cancer Res.* 2011 Oct 1;17(19):6304-12.
8. Higgins MJ, Baselga J. Targeted therapies for breast cancer. *J Clin Invest.* 2011 Oct; 121(10):3797-803
9. Cortes J, Calvo V, Ramirez-Merino N, O'Shaughnessy J, Brufsky A, Robert N, Vidal M, Muñoz E, Perez J, Dawood S, Saura C, Di Cosimo S, González-Martín A, Bellet M, Silva OE, Miles D, Llombart A, Baselga J. Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a meta-analysis. *Ann Oncol.* 2011 Oct 4.
10. Kostic AD, Gevers D, Pedamallu CS, Michaud M, Duke F, Earl AM, Ojesina AI, Jung J, Bass AJ, Tabernero J, Baselga J, Liu C, Shivdasani RA, Ogino S, Birren BW, Huttenhower C, Garrett WS, Meyerson M. Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma. *Genome Res.* 2012 Feb;22(2):292-8.
11. Sequist LV, Heist RS, Shaw AT, Fidias P, Rosovsky R, Temel JS, Lennes IT, Digumarthy S, Waltman BA, Bast E, Tammireddy S, Morrissey L, Muzikansky A, Goldberg SB, Gainor J, Channick CL, Wain JC, Gaissert H, Donahue DM, Muniappan A, Wright C, Willers H, Mathisen DJ, Choi NC, Baselga J, Lynch TJ, Ellisen LW, Mino-Kenudson M, Lanuti M, Borger DR, Iafrate AJ, Engelman JA, Dias-Santagata D. Implementing multiplexed genotyping of non-small-cell lung cancers into routine clinical practice. *Ann Oncol.* 2011 Dec; 22.
12. Rodrik-Outmezguine VS, Chandarlapaty S, Pagano NC, Poulidakos PI, Scaltriti M, Moskatel E, Baselga J, Guichard S, Rosen N. BIM expression in treatment naïve cancers predicts responsiveness to kinase inhibitors. *Cancer Discov.* 2011 Jun 17;1(3):248-59.
13. Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi GN. Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer. *N Engl J Med.* 2012 366(6):520-9.
14. Bendell JC, Rodon J, Burris HA, de Jonge M, Verweij J, Birlle D, Demanse D, De Buck SS, Ru QC, Peters M, Goldbrunner M, Baselga J. Phase I, Dose-Escalation Study of BKM120, an Oral Pan-Class I PI3K Inhibitor, in Patients With Advanced Solid Tumors. *J Clin Oncol.* 2012 30(3):282-90.

15. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, Roman L, Pedrini JL, Pienkowski T, Knott A, Clark E, Benyunes MC, Ross G, Swain SM; CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012 Jan 12;366(2):109-19.
16. Baselga J, Bradbury I, Eidtmann H, DeCosimo S, deAzambuja E, Aura C, Gomex H, Dinh P, Fauria K, Van Dooren V, Sktan G, Goldhirsch A, Chang TW, Horvath Z, Coccia-Portugal M, Dormont J, Tseng L, Kunz G, Sohn JH, Semiglazov V, Lerzo G, Palacova M, Probachai V, Puzstai L, Untch M, Gelber RD, Piccart M. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomized, open-label, multicentre, phase 3 trial. *Lancet*. 2012; Feb 18;379(9816):633-40
17. Eichhorn PJ, Rodon L, Gonzalez-Junca A, Dirac A, Gili M, Martinez-Saez E, Aura C, Barba I, Peg V, Prat A, Cuartas I, Jimenez J, Garcia-Dorado D, Sahuquillo J, Bernards R, Baselga J, Seoane J. USP15 stabilizes TGF-beta receptor I and promotes oncogenesis through the activation of TGF-beta signaling in glioblastoma. *Nat Med* 2012 Feb 19;18(3):429-35.
18. Markman B, Tabernero J, Krop I, Shapiro GI, Siu L, Chen LC, Mita M, Melendez Cuero M, Stutvoet S, Birle D, Anak O, Hackl W, Baselga J. Phase I safety, pharmacokinetic, and pharmacodynamic study of the oral phosphatidylinositol-3-kinase and mTOR inhibitor BGT226 in patients with advanced solid tumors. *Ann Onco* 2012 Feb 22.
19. Juric D, Baselga J. Tumor Genetic Testing for Patient Selection in Phase I Clinical Trials: The Case of PI3K Inhibitors. *J Clin Oncol* 2012 Mar 10;30(8):765-6
20. Metzger-Filho O, Tutt A, de Azambuja E, Saini KS, Viale G, Loi S, Bradbury I, Bliss JM, Azim HA Jr, Ellis P, Di Leo A, Baselga J, Sotiriou C, Piccart-Gebhart M. Dissecting the Heterogeneity of Triple-Negative Breast Cancer. *J Clin Oncol*. 2012 Mar 26.
21. Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW, Greninger P, Thompson IR, Luo X, Soares J, Liu Q, Iorio F, Surdez D, Chen L, Milano RJ, Bignell GR, Tam AT, Davies H, Stevenson JA, Barthorpe S, Lutz SR, Kogera F, Lawrence K, McLaren-Douglas A, Mitropoulos X, Mironenko T, Thi H, Richardson L, Zhou W, Jewitt F, Zhang T, O'Brien P, Boisvert JL, Price S, Hur W, Yang W, Deng X, Butler A, Choi HG, Chang JW, Baselga J, Stamenkovic I, Engelman JA, Sharma SV, Delattre O, Saez-Rodriguez J, Gray NS, Settleman J, Futreal PA, Haber DA, Stratton MR, Ramaswamy S, McDermott U, Benes CH. Systematic identification of genomic markers of drug sensitivity in cancer cells. *Nature*. 2012 Mar 28;483(7391):570-5
22. Hannon RA, Finkelman RD, Clack G, Iacona RB, Rimmer M, Gossiel F, Baselga J, Eastell R. Effects of Src kinase inhibition by saracatinib (AZD0530) on bone turnover in advanced malignancy in a Phase I study. *Bone*. 2012 Apr;50(4):885-92
23. Rodon J, Saura C, Dienstmann R, Vivancos A, Cjal SR, Baselga J, Tabernero J. Molecular prescreening to select patient population in early clinical trials. *Nat Rev Clin Oncol*. 2012 Apr 3. doi: 10.1038
24. Baselga J, Segalla JG, Roché H, Del Giglio A, Pinczowski H, Ciruelos EM, Filho SC, Gómez P, Van Eyll B, Bermejo B, Llombart A, Garicochea B, Durán MÁ, Hoff PM, Espié M, de Moraes AA, Ribeiro RA, Mathias C, Gil Gil M, Ojeda B, Morales J, Kwon Ro S, Li S, Costa F. Sorafenib in Combination With Capecitabine: An Oral Regimen for Patients With HER2-Negative Locally Advanced or Metastatic Breast Cancer. *J Clin Oncol*. 2012 May 1;30(13):1484-91
25. García-García C, Ibrahim YH, Serra V, Calvo MT, Guzmán M, Grueso J, Aura C, Pérez J, Jessen K, Liu Y, Rommel C, Tabernero J, Baselga J, Scaltriti M. Dual mTORC1/2 and HER2 Blockade Results in Antitumor Activity in Preclinical Models of Breast Cancer Resistant to Anti-HER2 Therapy. *Clin Cancer Res*. 2012 May 1;18(9):2603-12
26. Cortés J, Fumoleau P, Bianchi GV, Petrella TM, Gelmon K, Pivot X, Verma S, Albanell J, Conte P, Lluch A, Salvagni S, Servent V, Gianni L, Scaltriti M, Ross GA, Dixon J, Szado T, Baselga J. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2012 May 10;30(14):1594-600
27. Metzger-Filho O, Tutt A, de Azambuja E, Saini KS, Viale G, Loi S, Bradbury I, Bliss JM, Azim HA Jr, Ellis P, Di Leo A, Baselga J, Sotiriou C, Piccart-Gebhart M. Dissecting the heterogeneity of triple-negative breast cancer. *J Clin Oncol*. 2012 May 20;30(15):1879-87

**NARRATIVE REPORT ON CAREER AND RESEARCH INTERESTS:**

My career is focused towards the development of novel molecular targeted agents, with special emphasis in breast cancer. I have directed the pre-clinical and clinical development of therapies against the Epidermal Growth Factor Receptor (EGFR) and the closely related HER2 receptor. My current work has expanded towards the clinical development of mTOR and PI3Kinase inhibitors. In the process, I have been deeply involved in the creation of a new paradigm for translational and clinical research, generating hypotheses in the lab and moving them swiftly into clinical trials.

I have devoted 20 years to the development of anti-EGFR agents in the laboratory and in the clinic. I lead the initial clinical studies that identified the optimal dose and schedule of a series of EGFR agents. I was also the first one to report clinical activity with anti-EGFR (and anti-HER2) agents and have led the full clinical development of this class of agents. Our latest work is focused in triple negative breast cancer.

In the field of anti-HER2 therapies, I was the lead investigator in the first publication that demonstrated the clinical activity of the anti-HER2 monoclonal antibody trastuzumab (Herceptin) in patients with advanced HER2 over expressing breast cancer. I continue to lead state-of the art world-wide clinical trials with trastuzumab including in the neo-adjuvant and adjuvant setting. In the laboratory, I reported the synergy between paclitaxel and trastuzumab that lead to the registration clinical trial. We have also been able over the years to identify a number of mechanisms of resistance to anti-HER2 agents. Some of them including p95HER2 and hyper-activation of the PI3K-Akt-mTOR pathway are therapeutic targets themselves and we are exploring them. Our latest work includes the clinical development of novel anti-HER2 antibodies such as pertuzumab that have shown to improve the disease free survival and the overall survival in the first line setting. I am currently the principal investigator of the adjuvant clinical trial with pertuzumab.

I have pioneered the development of pharmacodynamic markers of target inhibition with signal transduction inhibitors in preclinical models and translated into early clinical trials where we sequentially interrogate tumors. Among a long list of findings, we observed that inhibition of mTOR induced intra-tumoral activation of compensatory feed back loops that resulted in activation of multiple pathways. In the lab and in the clinic we have established that the combined administration of rapamycin analogs and aromatase inhibitors results in improved outcome. We have also identified that the activation of compensatory pathways is mediated via the IGF-1R and clinical trials with anti-mTOR and anti-IGF-1R agents given combined have shown remarkable results in patients with Luminal B hormone refractory breast cancer. We have also led the conduct of clinical trials in patients with breast cancer harboring PI3K mutations.

On the administration front, I lead the transformation of the Vall d'Hebron Hospital in Barcelona from a small clinical service to a full cancer center with a large multidisciplinary research program and with the largest phase I program in Europe. I have recently moved to the Massachusetts General Hospital Cancer Center where I am implementing a newly designed strategic plan that has led to a robust growth of our patient volume, to the construction and acquisition of a number of satellites in Massachusetts, and to an unparalleled expansion of our phase I program. In addition, I have been instrumental in raising the funds, in the design and in the construction of a new Center for Targeted Therapies that will be inaugurated in October 2012.

In addition to my research and administrative functions described above, I have also been deeply involved in teaching. I established the first elective in oncology at the medical school in Barcelona in 1996 and I have also been involved in teaching of residents and fellows. At the European level, I created a number of International Fellowships during my ESMO presidency from which a large number of oncologists have benefited. At the societal level, I have been president of ESMO and a member of the board of director of both ASCO and AACR.

**IAAO2012 Title of the Talk:**

**Combinatorial Approaches against PI3 Kinase Pathway**