

## Title: Challenges with Drug Resistance



**Speaker**

### **Jeffrey A. Engelman, M.D., Ph.D.**

Principal Investigator, Research Laboratory, Massachusetts General Hospital (MGH) Cancer Center  
 Co-Leader, DFHCC Thoracic Program, Dana-Farber/Harvard Cancer Center  
 Director, Thoracic Oncology, MGH Cancer Center  
 Director, Molecular Therapeutics, MGH Cancer Center



**Chairman**

### **Nagahiro Saijo, M.D., Ph.D.**

Executive Officer of Japanese Society of Medical Oncology, Japan

### **Jeffrey A. Engelman, M.D., Ph.D.**

#### **EDUCATION:**

1993	B.A.	Chemistry	Northwestern University with honors
2000	M.D.	Medicine	Albert Einstein College of Medicine
2000	Ph.D.	Molecular Pharmacology (Dr. Michael Lisanti)	Albert Einstein College of Medicine

#### **CURRENT POSITION:**

04/2012-	Associate Professor	Medicine	Harvard Medical School
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#### **MAJOR ADMINISTRATIVE LEADERSHIP POSITIONS: LOCAL**

2008-	Principal Investigator, Research Laboratory	MGH Cancer Center
2009-	Co-Leader, DFHCC Thoracic Program	Dana-Farber/Harvard Cancer Center
2009-	Director, Thoracic Oncology	MGH Cancer Center
2012-	Director, Molecular Therapeutics	MGH Cancer Center

#### **HONORS AND PRIZES:**

2005	Young Investigator Award	American Society of Clinical Oncology
2005	Fellowship in Translational Lung	AACR-AstraZeneca Cancer Research and

	Cancer Research	Prevention Foundation
2007	Ellison Scholar Award	Massachusetts General Hospital
2008	Member of the One Hundred	Massachusetts General Hospital
2010	Team Science Award	AACR
2011	Stephen Krane Award	Massachusetts General Hospital Dept. of Medicine

## LATEST PUBLICATIONS:

- 1 Chakrabarty A, Rexer BN, Wang SE, Cook RS, Engelman JA, Arteaga CL. □H1047R phosphatidylinositol 3-kinase mutant enhances HER2-mediated transformation by heregulin production and activation of HER3. *Oncogene*. (2010). Jun 28. [Epub ahead of print]
- 2 Baba Y, Noshio K, Shima K, Meyerhardt JA, Chan AT, Engelman JA, Cantley LC, Loda M, Giovannucci E, Fuchs CS, Ogino S. Prognostic significance of AMP-activated protein kinase expression and modifying effect of MAPK3/1 in colorectal cancer. *Br J Cancer*. (2010). Sep 28;103(7):1025-33. Epub 2010 Aug 31
- 3 Corcoran RB, Dias-Santagata D, Bergethon K, Iafrate AJ, Settleman J, Engelman JA. BRAF gene amplification can promote acquired resistance to MEK inhibitors in cancer cells harboring the BRAF V600E mutation. *Science Signaling*. (2010). Nov 23;3(149):ra84.
- 4 Qi J, McTigue M, Rogers A, Lifshits E, Christensen J, Jänne P, Engelman JA. Acquisition of mutations and development of bypass tracks cause acquired resistance to MET inhibitors. *Cancer Research*. (2011). Published Online First January 25, 2011; doi:10.1158/0008-5472.CAN-10-1623.
- 5 Jänne PA, Boss DS, Camidge DR, Britten CD, Engelman JA, Garon EB, Guo F, Wong S, Liang J, Letrent S, Millham R, Taylor I, Eckhardt SG, Schellens JH. Phase I Dose-Escalation Study of the Pan-HER Inhibitor, PF299804, in Patients with Advanced Malignant Solid Tumors. *Clin Cancer Res*. (2011). Mar 1;17(5):1131-1139. Epub 2011 Jan 10.
- 6 Corcoran RB, Contino G, Deshpande V, Tzatsos A, Conrad C, Benes CH, Settleman J, Engelman A, Bardeesy N. STAT3 plays a critical role in KRAS-induced pancreatic tumorigenesis. *Cancer Research*. (2011). Jul 15;71(14):5020-9. Epub 2011 May 17.
- 7 Yonesaka K, Zejnullahu K, Okamoto I, Satoh T, Cappuzzo F, Souglakos J, Ercan D, Rogers A, Roncalli M, Takeda M, Fujisaka Y, Philips J, Shimizu T, Maenishi O, Cho Y, Sun J, Destro A, Taira K, Takeda K, Okabe T, Swanson J, Itoh H, Takada M, Lifshits E, Okuno K, Engelman JA, Shivdasani RA, Nishio K, Fukuoka M, Varella-Garcia M, Nakagawa K, Jänne PA. Activation of ERBB2 Signaling Causes Resistance to the EGFR-Directed Therapeutic Antibody Cetuximab. *Science Translational Medicine*. (2011). Sep 7;3(99):99ra86
- 8 Shaw AT, Yeap BY, Solomon BJ, Riely GJ, Gainor J, Engelman JA, Shapiro GI, Costa DB, Ou SH, Butaney M, Salgia R, Maki RG, Varella-Garcia M, Doebele RC, Bang YJ, Kulig K, Selaru P, Tang Y, Wilner KD, Kwak EL, Clark JW, Iafrate AJ, Camidge DR. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncology*. (2011) Oct;12(11):1004-12. Epub 2011 Sep 18.
- 9 Ramalingam SS, Spigel DR, Chen D, Steins MB, Engelman JA, Schneider CP, Novello S, Eberhardt WE, Crino L, Habben K, Liu L, Jänne PA, Brownstein CM, Reck M. Randomized Phase II Study of Erlotinib in Combination With Placebo or R1507, a Monoclonal Antibody to Insulin-Like Growth Factor-1 Receptor, for Advanced-Stage Non-Small-Cell Lung Cancer. *J Clin Oncol*. (2011). Dec 1;29 (34):4574-80. Epub 2011 Oct 24.
- 10 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):2616-24. Epub 2011 Nov 9.
- 11 Ebi H, Corcoran RB, Singh A, Chen Z, Song Y, Lifshits E, Ryan DP, Meyerhardt J, Benes C, Settleman J, Wong K, Cantley L, Engelman JA. Receptor tyrosine kinases exert dominant control over PI3K signaling in human KRAS mutant colorectal cancers. *Journal of Clinical Investigation*. (2011). Oct 10. pii: 57909. doi: 10.1172/JCI57909. [Epub ahead of print]
- 12 Faber AC, Corcoran RB, Ebi H, Sequist LV, Waltman BA, Chung E, Incio J, Digumarthy SA, Pollack SF, Song YC, Muzinkansky A, Lifshits E, Roberge S, Coffman EJ, Benes CH, Gomez H, Baselga J, Arteaga CL, Rivera MN, Dias-Santagata D, Jain RK, and Engelman JA. BIM expression in treatment naïve cancers predicts responsiveness to kinase inhibitors. *Cancer Discovery*. (2011). July 22, 2011 CD-11-0106; Published Online First July 22, 2011; doi:10.1158/2159-8290.CD-11-0106.

- 13 Bergethon K, Shaw AT, Ignatius Ou SH, Katayama R, Lovly CM, McDonald NT, Massion PP, Siwak-Tapp C, Gonzalez A, Fang R, Mark EJ, Batten JM, Chen H, Wilner KD, Kwak EL, Clark JW, Carbone DP, Ji H, Engelman JA, Mino-Kenudson M, Pao W, Iafrate AJ. ROS1 Rearrangements Define a Unique Molecular Class of Lung Cancers. *Journal of Clinical Oncology*. (2012). Jan 3. [Epub ahead of print]
- 14 Corcoran RB, Ebi H, Turke AB, Coffee EM, Nishino M, Cogdill AP, Brown RD, Delle Pelle P, Dias-Santagata D, Hung KE, Flaherty KT, Piris A, Wargo JA, Settleman J, Mino-Kenudson M, and Engelman JA. EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition. *Cancer Discovery*. (2012). Published OnlineFirst January 16, 2012; doi: 10.1158/2159-8290.CD-11-0341
- 15 Katayama R, Shaw AT, Khan TM, Mino-Kenudson M, Solomon BJ, Halmos B, Jessop N, Wain JC, Yeo AT, Benes C, Drew L, Saeh JC, Crosby K, Sequist LV, Iafrate AJ, Engelman JA. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. *Science Translational Medicine*. (2012). Sci Transl Med. 2012 Feb 8;4(120):120ra17. Epub 2012 Jan 25.
- 16 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. doi: 10.1038/nature11005.
- 17 Chen Z, Cheng K, Walton Z, Wang Y, Ebi H, Shimamura T, Liu Y, Tupper T, Ouyang J, Li J, Gao P, Woo MS, Xu C, Yanagita M, Altabef A, Wang S, Lee C, Nakada Y, Peña CG, Sun Y, Franchetti Y, Yao C, Saur A, Cameron MD, Nishino M, Hayes DN, Wilkerson MD, Roberts PJ, Lee CB, Bardeesy N, Butaney M, Chirieac LR, Costa DB, Jackman D, Sharpless NE, Castrillon DH, Demetri GD, Jänne PA, Pandolfi PP, Cantley LC, Kung AL, Engelman JA, Wong KK. A murine lung cancer co-clinical trial identifies genetic modifiers of therapeutic response. *Nature*. (2012) Mar 18;483(7391):613-7. doi: 10.1038/nature10937.
- 18 Nardi V, Song Y, Santamaria-Barria JA, Cospes AK, Lam Q, Faber AC, Boland GM, Yeap BY, Bergethon K, Scialabba VL, Tsao H, Settleman J, Ryan DP, Borger DR, Bhan AK, Hoang MP, Iafrate AJ, Cusack JC, Engelman JA, Dias-Santagata D. Activation of PI3K signaling in Merkel cell carcinoma. *Clinical Cancer Research*. (2012) Mar 1;18(5):1227-36. Epub 2012 Jan 18.

## CURRENT INTEREST:

The overarching aim of research in the Engelman laboratory is to develop new and more effective therapeutic strategies for the treatment of cancer, with a particular emphasis on lung cancer. Cancer therapies are changing from general chemotherapeutic agents to drugs that target specific proteins and signaling pathways (i.e. targeted therapies). My laboratory aims to understand the biological underpinnings of cancer sensitivity and resistance to this emerging class of therapies. We are particularly interested in the regulation of the PI3K pathway, a signaling network that is crucial for the growth and survival of many epithelial cancers. The ultimate goal of our research is to develop therapies that are more effective and less toxic for patients with cancer.

**IAAO2012 Title of the Talk:**

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