

- JP, Kallioniemi O, Screpanti I, Poellinger L, Sahlgren C, Lendahl U. Non-canonical Notch signaling activates IL-6/JAK/STAT signaling in breast tumor cells and is controlled by p53 and IKKalpha/IKKbeta. *Oncogene* 2013;32:4892-902.
4. Kwon C, Cheng P, King IN, Andersen P, Shenje L, Nigam V, Srivastava D. Notch post-translationally regulates beta-catenin protein in stem and progenitor cells. *Nat Cell Biol* 2011;13:1244-51.
 5. Perumalsamy LR, Nagala M, Banerjee P, Sarin A. A hierarchical cascade activated by non-canonical Notch signaling and the mTOR-Rictor complex regulates neglect-induced death in mammalian cells. *Cell Death Differ* 2009;16:879-89.
 6. Shin HM, Tilahun ME, Cho OH, Chandiran K, Kuksin CA, Keerthivasan S, Fauq AH, Golde TE, Miele L, Thome M, Osborne BA, Minter LM. NOTCH1 can initiate NF-kappaB activation via cytosolic interactions with components of the T cell signalosome. *Front Immunol* 2014;5:249.
 7. Bocchetta M, Miele L, Pass HI, Carbone M. Notch-1 induction, a novel activity of SV40 required for growth of SV40-transformed human mesothelial cells. *Oncogene* 2003;22:81-9.
 8. Carter Y, Jaskula-Sztul R, Chen H, Mazeh H. Signaling pathways as specific pharmacologic targets for neuroendocrine tumor therapy: RET, PI3K, MEK, growth factors, and Notch. *Neuroendocrinology* 2013;97:57-66.
 9. Hassan WA, Yoshida R, Kudoh S, Hasegawa K, Niimori-Kita K, Ito T. Notch1 controls cell invasion and metastasis in small cell lung carcinoma cell lines. *Lung Cancer* 2014;86:304-10.
 10. Krausch M, Kroepil F, Lehwald N, Lachenmayer A, Schott M, Anlauf M, Cupisti K, Knoefel WT, Raffel A. Notch 1 tumor expression is lacking in highly proliferative pancreatic neuroendocrine tumors. *Endocrine* 2013;44:182-6.
 11. Kunnimalaiyaan M, Chen H. Tumor suppressor role of Notch-1 signaling in neuroendocrine tumors. *Oncologist* 2007;12:535-42.
 12. Kunnimalaiyaan M, Yan S, Wong F, Zhang YW, Chen H. Hairly Enhancer of Split-1 (HES-1), a Notch1 effector, inhibits the growth of carcinoid tumor cells. *Surgery* 2005;138:1137-42; discussion 42.
 13. Meder L, Konig K, Ozretic L, Schultheis AM, Ueckerthof F, Ade CP, Albus K, Boehm D, Rommelscheidt-Fuss U, Florin A, Buhl T, Hartmann W, Wolf J, Merkelbach-Bruse S, Eilers M, Perner S, Heukamp LC, Buettner R. NOTCH, ASCL1, p53 and RB alterations define an alternative pathway driving neuroendocrine and small cell lung carcinomas. *Int J Cancer* 2016;138:927-38.
 14. Saunders LR, Bankovich AJ, Anderson WC, Aujay MA, Bheddah S, Black K, Desai R, Escarpe PA, Hampl J, Laysang A, Liu D, Lopez-Molina J, Milton M, Park A, Pysz MA, Shao H, Slingerland B, Torgov M, Williams SA, Foord O, Howard P, Jassem J, Badzio A, Czapiewski P, Harpole DH, Dowlati A, Massion PP, Travis WD, Pietanza MC, Poirier JT, Rudin CM, Stull RA, Dylla SJ. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells *in vivo*. *Sci Transl Med* 2015;7:302ra136.
 15. Andersson ER, Lendahl U. Therapeutic modulation of Notch signalling -- are we there yet? *Nat Rev Drug Discov* 2014;13:357-78.
 16. Chikara S, Reindl KM. Notch signaling: a hero or villain in the war against cancer? *Transl Lung Cancer Res* 2013;2:449-51.
 17. D'Souza B, Miyamoto A, Weinmaster G. The many facets of Notch ligands. *Oncogene* 2008;27:5148-67.
 18. Espinoza I, Miele L. Notch inhibitors for cancer treatment. *Pharmacol Ther* 2013;139:95-110.
 19. Hirata N, Yamada S, Shoda T, Kurihara M, Sekino Y, Kanda Y. Sphingosine-1-phosphate promotes expansion of cancer stem cells via S1PR3 by a ligand-independent Notch activation. *Nat Commun* 2014;5:4806.
 20. Andersen P, Uosaki H, Shenje LT, Kwon C. Non-canonical Notch signaling: emerging role and mechanism. *Trends Cell Biol* 2012;22:257-65.
 21. Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011;40:1-18, vii.
 22. Nicolas M, Wolfer A, Raj K, Kummer JA, Mill P, van Noort M, Hui CC, Clevers H, Dotto GP, Radtke F. Notch1 functions as a tumor suppressor in mouse skin. *Nat Genet* 2003;33:416-21.
 23. Dongre A, Surampudi L, Lawlor RG, Fauq AH, Miele L, Golde TE, Minter LM, Osborne BA. Non-Canonical Notch Signaling Drives Activation and Differentiation of Peripheral CD4(+) T Cells. *Front Immunol* 2014;5:54.
 24. Minter LM, Osborne BA. Canonical and non-canonical Notch signaling in CD4(+) T cells. *Curr Top Microbiol Immunol* 2012;360:99-114.
 25. Meurette O, Stylianou S, Rock R, Collu GM, Gilmore AP, Brennan K. Notch activation induces Akt signaling via an autocrine loop to prevent apoptosis in breast epithelial cells. *Cancer Res* 2009;69:5015-22.
 26. Crabtree JS, Singleton CS, Miele L. Notch Signaling in Neuroendocrine Tumors. *Front Oncol* 2016;6:94.
 27. Borggrete T, Oswald F. The Notch signaling pathway: transcriptional regulation at Notch target genes. *Cell Mol Life Sci* 2009;66:1631-46.
 28. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, Diaz-Perez JA, Martinez Del Prado MP, Alonso Orduna V, Sevilla-Garcia I, Villabona-Artero C, Beguiristain-Gomez A, Llanos-Munoz M, Marazuela M, Alvarez-Escola C, Castellano D, Vilar E, Jimenez-Fonseca P, Teule A, Sastre-Valera J, Benavent-Vinuelas M, Monleon A, Salazar R. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). *Ann Oncol* 2010;21:1794-803.
 29. Mocellin S, Nitti D. Gastrointestinal carcinoid: epidemiological and survival evidence from a large population-based study (n = 25 531). *Ann Oncol* 2013;24:3040-4.
 30. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008;26:3063-72.
 31. Klimstra DS, Modlin IR, Adsay NV, Chetty R, Deshpande V, Gonen M, Jensen RT, Kidd M, Kulke MH, Lloyd RV, Moran C, Moss SF, Oberg K, O'Toole D, Rindi G, Robert ME, Suster S, Tang LH, Tzen CY, Washington MK, Wiedenmann B, Yao J. Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. *Am J Surg Pathol* 2010;34:300-13.
 32. Strosberg J. Neuroendocrine tumours of the small intestine. *Best Pract Res Clin Gastroenterol* 2012;26:755-73.
 33. Kunz PL. Carcinoid and Neuroendocrine Tumors: Building on Success. *J Clin Oncol* 2015;33:1855-63.
 34. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: neuroendocrine tumors v, 2016. Updated 5/25/2016, accessed 7/28/16. In.
 35. Susini C, Buscail L. Rationale for the use of somatostatin analogs as antitumor agents. *Ann Oncol* 2006;17:1733-42.
 36. Cives M, Strosberg J. The expanding role of somatostatin analogs in gastroenteropancreatic and lung neuroendocrine tumors. *Drugs* 2015;75:847-58.
 37. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Blaker M, Harder J, Arnold C, Gress T, Arnold R, Group PS. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009;27:4656-63.
 38. Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, Cadiot G, Wolin EM, Capdevila J, Wall L, Rindi G, Langley A, Martinez S, Blumberg J, Ruzniewski P, Investigators C. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J*

Med 2014;371:224-33.

39. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG, Tomassetti P, Pavel ME, Hoosen S, Haas T, Lincy J, Lebwohl D, Oberg K, Rad001 in Advanced Neuroendocrine Tumors TTSG. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:514-23.
40. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, Valle J, Metrakos P, Smith D, Vinik A, Chen JS, Horsch D, Hammel P, Wiedenmann B, Van Cutsem E, Patyna S, Lu DR, Blankmeester C, Chao R, Ruzsiewicz P. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:501-13.
41. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, Tomasek J, Raderer M, Lahner H, Voi M, Pacaud LB, Rouyrre N, Sachs C, Valle JW, Delle Fave G, Van Cutsem E, Tesselaer M, Shimada Y, Oh DY, Strosberg J, Kulke MH, Pavel ME, Rad001 in Advanced Neuroendocrine Tumours FTSG. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016;387:968-77.
42. Jiao Y, Shi C, Edil BH, de Wilde RF, Klimstra DS, Maitra A, Schulick RD, Tang LH, Wolfgang CL, Choti MA, Velculescu VE, Diaz LA, Jr., Vogelstein B, Kinzler KW, Hruban RH, Papadopoulos N. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science* 2011;331:1199-203.
43. Banck MS, Kanwar R, Kulkarni AA, Boora GK, Metge F, Kipp BR, Zhang L, Thorland EC, Minn KT, Tentu R, Eckloff BW, Wieben ED, Wu Y, Cunningham JM, Nagorney DM, Gilbert JA, Ames MM, Beutler AS. The genomic landscape of small intestine neuroendocrine tumors. *J Clin Invest* 2013;123:2502-8.
44. Francis JM, Kiezun A, Ramos AH, Serra S, Pedamallu CS, Qian ZR, Banck MS, Kanwar R, Kulkarni AA, Karpathakis A, Manzo V, Contractor T, Phillips J, Nickerson E, Pho N, Hooshmand SM, Brais LK, Lawrence MS, Pugh T, McKenna A, Sivachenko A, Cibulskis K, Carter SL, Ojesina AI, Freeman S, Jones RT, Voet D, Saksena G, Auclair D, Onofrio R, Shefler E, Sougnez C, Grimsby J, Green L, Lennon N, Meyer T, Caplin M, Chung DC, Beutler AS, Ogino S, Thirlwell C, Shivdasani R, Asa SL, Harris CR, Getz G, Kulke M, Meyerson M. Somatic mutation of CDKN1B in small intestine neuroendocrine tumors. *Nat Genet* 2013;45:1483-6.
45. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. *Nature* 2001;414:105-11.
46. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. *Proc Natl Acad Sci U S A* 2003;100:3983-8.
47. Li C, Heidt DG, Dalerba P, Burant CF, Zhang L, Adsay V, Wicha M, Clarke MF, Simeone DM. Identification of pancreatic cancer stem cells. *Cancer Res* 2007;67:1030-7.
48. Yang ZF, Ho DW, Ng MN, Lau CK, Yu WC, Ngai P, Chu PW, Lam CT, Poon RT, Fan ST. Significance of CD90+ cancer stem cells in human liver cancer. *Cancer Cell* 2008;13:153-66.
49. Lapidot T, Sirard C, Vormoor J, Murdoch B, Hoang T, Caceres-Cortes J, Minden M, Paterson B, Caligiuri MA, Dick JE. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. *Nature* 1994;367:645-8.
50. Gaur P, Sceusi EL, Samuel S, Xia L, Fan F, Zhou Y, Lu J, Tozzi F, Lopez-Berestein G, Vivas-Mejia P, Rashid A, Fleming JB, Abdalla EK, Curley SA, Vauthey JN, Sood AK, Yao JC, Ellis LM. Identification of cancer stem cells in human gastrointestinal carcinoid and neuroendocrine tumors. *Gastroenterology* 2011;141:1728-37.
51. Krampitz GW, George BM, Willingham SB, Volkmer JP, Weiskopf K, Jahchan N, Newman AM, Sahoo D, Zemek AJ, Yanovsky RL, Nguyen JK, Schnorr PJ, Mazur PK, Sage J, Longacre TA, Visser BC, Poultsides GA, Norton JA, Weissman IL. Identification of tumorigenic cells and therapeutic targets in pancreatic neuroendocrine tumors. *Proc Natl Acad Sci U S A* 2016;113:4464-9.
52. Louvi A, Artavanis-Tsakonas S. Notch signalling in vertebrate neural development. *Nat Rev Neurosci* 2006;7:93-102.
53. Artavanis-Tsakonas S, Rand MD, Lake RJ. Notch signaling: cell fate control and signal integration in development. *Science* 1999;284:770-6.
54. Kunnimalaiyaan M, Traeger K, Chen H. Conservation of the Notch1 signaling pathway in gastrointestinal carcinoid cells. *Am J Physiol Gastrointest Liver Physiol* 2005;289:G636-42.
55. Kunnimalaiyaan M, Vaccaro AM, Ndiaye MA, Chen H. Overexpression of the NOTCH1 intracellular domain inhibits cell proliferation and alters the neuroendocrine phenotype of medullary thyroid cancer cells. *J Biol Chem* 2006;281:39819-30.
56. Nakakura EK, Sriuranpong VR, Kunnimalaiyaan M, Hsiao EC, Schuebel KE, Borges MW, Jin N, Collins BJ, Nelkin BD, Chen H, Ball DW. Regulation of neuroendocrine differentiation in gastrointestinal carcinoid tumor cells by notch signaling. *J Clin Endocrinol Metab* 2005;90:4350-6.
57. Shida T, Furuya M, Nikaido T, Hasegawa M, Koda K, Oda K, Miyazaki M, Kishimoto T, Nakatani Y, Ishikura H. Sonic Hedgehog-Gli1 signaling pathway might become an effective therapeutic target in gastrointestinal neuroendocrine carcinomas. *Cancer Biol Ther* 2006;5:1530-8.
58. Wang H, Chen Y, Fernandez-Del Castillo C, Yilmaz O, Deshpande V. Heterogeneity in signaling pathways of gastroenteropancreatic neuroendocrine tumors: a critical look at notch signaling pathway. *Mod Pathol* 2013;26:139-47.
59. Kao HY, Ordentlich P, Koyano-Nakagawa N, Tang Z, Downes M, Kintner CR, Evans RM, Kadesch T. A histone deacetylase corepressor complex regulates the Notch signal transduction pathway. *Genes Dev* 1998;12:2269-77.
60. Mulligan P, Yang F, Di Stefano L, Ji JY, Ouyang J, Nishikawa JL, Toiber D, Kulkarni M, Wang Q, Najafi-Shoushtari SH, Mostoslavsky R, Gygi SP, Gill G, Dyson NJ, Naar AM. A SIRT1-LSD1 corepressor complex regulates Notch target gene expression and development. *Mol Cell* 2011;42:689-99.
61. Wang J, Scully K, Zhu X, Cai L, Zhang J, Prefontaine GG, Kronen A, Ohgi KA, Zhu P, Garcia-Bassets I, Liu F, Taylor H, Lozach J, Jayes FL, Korach KS, Glass CK, Fu XD, Rosenfeld MG. Opposing LSD1 complexes function in developmental gene activation and repression programmes. *Nature* 2007;446:882-7.
62. Borggrefe T, Liefke R. Fine-tuning of the intracellular canonical Notch signaling pathway. *Cell Cycle* 2012;11:264-76.
63. Liefke R, Oswald F, Alvarado C, Ferres-Marco D, Mittler G, Rodriguez P, Dominguez M, Borggrefe T. Histone demethylase KDM5A is an integral part of the core Notch-RBP-J repressor complex. *Genes Dev* 2010;24:590-601.
64. Miele L. Transcription factor RBPJ/CSL: a genome-wide look at transcriptional regulation. *Proc Natl Acad Sci U S A* 2011;108:14715-6.
65. Wang H, Zou J, Zhao B, Johannsen E, Ashworth T, Wong H, Pear WS, Schug J, Blacklow SC, Arnett KL, Bernstein BE, Kieff E, Aster JC. Genome-wide analysis reveals conserved and divergent features of Notch1/RBPJ binding in human and murine T-lymphoblastic leukemia cells. *Proc Natl Acad Sci U S A* 2011;108:14908-13.
66. Zhao B, Zou J, Wang H, Johannsen E, Peng CW, Quackenbush J, Mar JC, Morton CC, Freedman ML, Blacklow SC, Aster JC, Bernstein BE, Kieff E. Epstein-Barr virus exploits intrinsic B-lymphocyte transcription programs to achieve immortal cell growth. *Proc Natl Acad Sci U S A* 2011;108:14902-7.
67. Swarts DR, Ramaekers FC, Speel EJ. Molecular and cellular biology of neuroendocrine lung tumors: evidence for separate biological entities. *Biochim Biophys Acta* 2012;1826:255-71.
68. Travis WD. The 2015 WHO classification of lung tumors. *Pathologie* 2014;35 Suppl 2:188.
69. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO

Classification of Tumours of the Lung, Pleura, Thymus and Heart. 4th edition. In. Lyon France: International Agency for Research on Cancer; 2015.

70. Travis WD. Advances in neuroendocrine lung tumors. *Ann Oncol* 2010;21 Suppl 7:vii65-71.
71. Dettterbeck FC. Management of carcinoid tumors. *Ann Thorac Surg* 2010;89:998-1005.
72. Besse B, Heist RS, Papadimitrakopoulou VA, Camidge DR, Beck JT, Schmid P, Mulatero C, Miller N, Dimitrijevic S, Urva S, Pylvaenäinen I, Petrovic K, Johnson BE. A phase Ib dose-escalation study of everolimus combined with cisplatin and etoposide as first-line therapy in patients with extensive-stage small-cell lung cancer. *Ann Oncol* 2014;25:505-11.
73. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Horsch D, Winkler RE, Klimovsky J, Lebwohl D, Jehl V, Wolin EM, Oberg K, Van Cutsem E, Yao JC, Group R-S. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011;378:2005-12.
74. Han JY, Kim HY, Lim KY, Han JH, Lee YJ, Kwak MH, Kim HJ, Yun T, Kim HT, Lee JS. A phase II study of sunitinib in patients with relapsed or refractory small cell lung cancer. *Lung Cancer* 2013;79:137-42.
75. Johnson BE, Fischer T, Fischer B, Dunlop D, Rischin D, Silberman S, Kowalski MO, Sayles D, Dimitrijevic S, Fletcher C, Hornick J, Salgia R, Le Chevalier T. Phase II study of imatinib in patients with small cell lung cancer. *Clin Cancer Res* 2003;9:5880-7.
76. Shibata T, Kokubu A, Tsuta K, Hirohashi S. Oncogenic mutation of PIK3CA in small cell lung carcinoma: a potential therapeutic target pathway for chemotherapy-resistant lung cancer. *Cancer Lett* 2009;283:203-11.
77. Tatematsu A, Shimizu J, Murakami Y, Horio Y, Nakamura S, Hida T, Mitsudomi T, Yatabe Y. Epidermal growth factor receptor mutations in small cell lung cancer. *Clin Cancer Res* 2008;14:6092-6.
78. Wistuba II, Gazdar AF, Minna JD. Molecular genetics of small cell lung carcinoma. *Semin Oncol* 2001;28:3-13.
79. Wakuda K, Kenmotsu H, Serizawa M, Koh Y, Isaka M, Takahashi S, Ono A, Taira T, Naito T, Murakami H, Mori K, Endo M, Nakajima T, Ohde Y, Takahashi T, Yamamoto N. Molecular profiling of small cell lung cancer in a Japanese cohort. *Lung Cancer* 2014;84:139-44.
80. Iwakawa R, Takenaka M, Kohno T, Shimada Y, Totoki Y, Shibata T, Tsuta K, Nishikawa R, Noguchi M, Sato-Otsubo A, Ogawa S, Yokota J. Genome-wide identification of genes with amplification and/or fusion in small cell lung cancer. *Genes Chromosomes Cancer* 2013;52:802-16.
81. Peifer M, Fernandez-Cuesta L, Sos ML, George J, Seidel D, Kasper LH, Plenker D, Leenders F, Sun R, Zander T, Menon R, Koker M, Dahmen I, Muller C, Di Cerbo V, Schildhaus HU, Altmuller J, Baessmann I, Becker C, de Wilde B, Vandesompele J, Bohm D, Ansen S, Gabler F, Wilkening I, Heynck S, Heuckmann JM, Lu X, Carter SL, Cibulskis K, Banerji S, Getz G, Park KS, Rauh D, Grutter C, Fischer M, Pasqualucci L, Wright G, Wainer Z, Russell P, Petersen I, Chen Y, Stoelben E, Ludwig C, Schnabel P, Hoffmann H, Muley T, Brockmann M, Engel-Riedel W, Muscarella LA, Fazio VM, Groen H, Timens W, Sietsma H, Thunnissen E, Smit E, Heideman DA, Snijders PJ, Cappuzzo F, Ligorio C, Damiani S, Field J, Solberg S, Brustugun OT, Lund-Iversen M, Sanger J, Clement JH, Soltermann A, Moch H, Weder W, Solomon B, Soria JC, Validire P, Besse B, Brambilla E, Brambilla C, Lantuejoul S, Lorimier P, Schneider PM, Hallek M, Pao W, Meyerson M, Sage J, Shendure J, Schneider R, Buttner R, Wolf J, Nurnberg P, Perner S, Heukamp LC, Brindle PK, Haas S, Thomas RK. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet* 2012;44:1104-10.
82. Rudin CM, Durinck S, Stawiski EW, Poirier JT, Modrusan Z, Shames DS, Bergbower EA, Guan Y, Shin J, Guillory J, Rivers CS, Foo CK, Bhatt D, Stinson J, Gnad F, Haverty PM, Gentleman R, Chaudhuri S, Janakiraman V, Jaiswal BS, Parikh C, Yuan W, Zhang Z, Koeppen H, Wu TD, Jansen HM, Yauch RL, Huffman KE, Paskulin DD, Illei PB, Varela-Garcia M, Gazdar AF, de Sauvage FJ, Bourgon R, Minna JD, Brock MV, Seshagiri S. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. *Nat Genet* 2012;44:1111-6.
83. Fernandez-Cuesta L, Peifer M, Lu X, Sun R, Ozretic L, Seidel D, Zander T, Leenders F, George J, Muller C, Dahmen I, Pinther B, Bosco G, Konrad K, Altmuller J, Nurnberg P, Achter V, Lang U, Schneider PM, Bogus M, Soltermann A, Brustugun OT, Helland A, Solberg S, Lund-Iversen M, Ansen S, Stoelben E, Wright GM, Russell P, Wainer Z, Solomon B, Field JK, Hyde R, Davies MP, Heukamp LC, Petersen I, Perner S, Lovly CM, Cappuzzo F, Travis WD, Wolf J, Vingron M, Brambilla E, Haas SA, Buettner R, Thomas RK. Frequent mutations in chromatin-remodelling genes in pulmonary carcinoids. *Nat Commun* 2014;5:3518.
84. George J, Lim JS, Jang SJ, Cun Y, Ozretic L, Kong G, Leenders F, Lu X, Fernandez-Cuesta L, Bosco G, Muller C, Dahmen I, Jahchan NS, Park KS, Yang D, Karnezis AN, Vaka D, Torres A, Wang MS, Korbel JO, Menon R, Chun SM, Kim D, Wilkerson M, Hayes N, Engelmann D, Putzer B, Bos M, Michels S, Vlastic I, Seidel D, Pinther B, Schaub P, Becker C, Altmuller J, Yokota J, Kohno T, Iwakawa R, Tsuta K, Noguchi M, Muley T, Hoffmann H, Schnabel PA, Petersen I, Chen Y, Soltermann A, Tischler V, Choi CM, Kim YH, Massion PP, Zou Y, Jovanovic D, Kontic M, Wright GM, Russell PA, Solomon B, Koch I, Lindner M, Muscarella LA, la Torre A, Field JK, Jakopovic M, Knezevic J, Castanos-Velez E, Roz L, Pastorino U, Brustugun OT, Lund-Iversen M, Thunnissen E, Kohler J, Schuler M, Botling J, Sandelin M, Sanchez-Cespedes M, Salvesen HB, Achter V, Lang U, Bogus M, Schneider PM, Zander T, Ansen S, Hallek M, Wolf J, Vingron M, Yatabe Y, Travis WD, Nurnberg P, Reinhardt C, Perner S, Heukamp L, Buttner R, Haas SA, Brambilla E, Peifer M, Sage J, Thomas RK. Comprehensive genomic profiles of small cell lung cancer. *Nature* 2015;524:47-53.
85. Salcido CD, Larochele A, Taylor BJ, Dunbar CE, Varticovski L. Molecular characterisation of side population cells with cancer stem cell-like characteristics in small-cell lung cancer. *Br J Cancer* 2010;102:1636-44.
86. Wang P, Gao Q, Suo Z, Munthe E, Solberg S, Ma L, Wang M, Westerdaal NA, Kvalheim G, Gaudernack G. Identification and characterization of cells with cancer stem cell properties in human primary lung cancer cell lines. *PLoS One* 2013;8:e57020.
87. Eramo A, Lotti F, Sette G, Pilozzi E, Biffoni M, Di Virgilio A, Conticello C, Ruco L, Peschle C, De Maria R. Identification and expansion of the tumorigenic lung cancer stem cell population. *Cell Death Differ* 2008;15:504-14.
88. Qiu X, Wang Z, Li Y, Miao Y, Ren Y, Luan Y. Characterization of sphere-forming cells with stem-like properties from the small cell lung cancer cell line H446. *Cancer Lett* 2012;323:161-70.
89. Roudi R, Korourian A, Sharifabrizi A, Madjd Z. Differential expression of cancer stem cell markers ALDH1 and CD133 in various lung cancer subtypes. *Cancer Invest* 2015;33:294-302.
90. Sarvi S, Mackinnon AC, Avlonitis N, Bradley M, Rintoul RC, Rassl DM, Wang W, Forbes SJ, Gregory CD, Sethi T. CD133+ cancer stem-like cells in small cell lung cancer are highly tumorigenic and chemoresistant but sensitive to a novel neuropeptide antagonist. *Cancer Res* 2014;74:1554-65.
91. Wang B, Yang H, Huang YZ, Yan RH, Liu FJ, Zhang JN. Biologic characteristics of the side population of human small cell lung cancer cell line H446. *Chin J Cancer* 2010;29:254-60.
92. Zhang Z, Zhou Y, Qian H, Shao G, Lu X, Chen Q, Sun X, Chen D, Yin R, Zhu H, Shao Q, Xu W. Stemness and inducing differentiation of small cell lung cancer NCI-H446 cells. *Cell Death Dis* 2013;4:e633.
93. Kolev VN, Wright QG, Vidal CM, Ring JE, Shapiro IM, Ricono J, Weaver DT, Padval MV, Pachter JA, Xu Q. PI3K/mTOR dual

- inhibitor VS-5584 preferentially targets cancer stem cells. *Cancer Res* 2015;75:446-55.
94. Elias S, Liang S, Chen Y, De Marco MA, Machek O, Skucha S, Miele L, Bocchetta M. Notch-1 stimulates survival of lung adenocarcinoma cells during hypoxia by activating the IGF-1R pathway. *Oncogene* 2010;29:2488-98.
 95. Sriuranpong V, Borges MW, Ravi RK, Arnold DR, Nelkin BD, Baylin SB, Ball DW. Notch signaling induces cell cycle arrest in small cell lung cancer cells. *Cancer Res* 2001;61:3200-5.
 96. Zhou M, Jin WY, Fan ZW, Han RC. Analysis of the expression of the Notch3 receptor protein in adult lung cancer. *Oncol Lett* 2013;5:499-504.
 97. Ito T, Udaka N, Yazawa T, Okudela K, Hayashi H, Sudo T, Guillemot F, Kageyama R, Kitamura H. Basic helix-loop-helix transcription factors regulate the neuroendocrine differentiation of fetal mouse pulmonary epithelium. *Development* 2000;127:3913-21.
 98. Morimoto M, Nishinakamura R, Saga Y, Kopan R. Different assemblies of Notch receptors coordinate the distribution of the major bronchial Clara, ciliated and neuroendocrine cells. *Development* 2012;139:4365-73.
 99. Yen WC, Fischer MM, Axelrod F, Bond C, Cain J, Cancilla B, Henner WR, Meisner R, Sato A, Shah J, Tang T, Wallace B, Wang M, Zhang C, Kapoun AM, Lewicki J, Gurney A, Hoey T. Targeting Notch signaling with a Notch2/Notch3 antagonist (tarextumab) inhibits tumor growth and decreases tumor-initiating cell frequency. *Clin Cancer Res* 2015;21:2084-95.
 100. Graziani I, Elias S, De Marco MA, Chen Y, Pass HI, De May RM, Strack PR, Miele L, Bocchetta M. Opposite effects of Notch-1 and Notch-2 on mesothelioma cell survival under hypoxia are exerted through the Akt pathway. *Cancer Res* 2008;68:9678-85.
 101. Yun J, Pannuti A, Espinoza I, Zhu H, Hicks C, Zhu X, Caskey M, Rizzo P, D'Souza G, Backus K, Denning MF, Coon J, Sun M, Bresnick EH, Osipo C, Wu J, Strack PR, Tonetti DA, Miele L. Crosstalk between PKCalpha and Notch-4 in endocrine-resistant breast cancer cells. *Oncogenesis* 2013;2:e60.
 102. Parr C, Watkins G, Jiang WG. The possible correlation of Notch-1 and Notch-2 with clinical outcome and tumour clinicopathological parameters in human breast cancer. *Int J Mol Med* 2004;14:779-86.
 103. Sun J, Deng WM. Notch-dependent downregulation of the homeodomain gene cut is required for the mitotic cycle/endocycle switch and cell differentiation in *Drosophila* follicle cells. *Development* 2005;132:4299-308.
 104. Osipo C, Golde TE, Osborne BA, Miele LA. Off the beaten pathway: the complex cross talk between Notch and NF-kappaB. *Lab Invest* 2008;88:11-7.
 105. Raafat A, Lawson S, Bargo S, Klauzinska M, Strizzi L, Goldhar AS, Buono K, Salomon D, Vonderhaar BK, Callahan R. Rbpj conditional knockout reveals distinct functions of Notch4/Int3 in mammary gland development and tumorigenesis. *Oncogene* 2009;28:219-30.
 106. Robinson DR, Kalyana-Sundaram S, Wu YM, Shankar S, Cao X, Ateeq B, Asangani IA, Iyer M, Maher CA, Grasso CS, Lonigro RJ, Quist M, Siddiqui J, Mehra R, Jing X, Giordano TJ, Sabel MS, Kleer CG, Palanisamy N, Natrajan R, Lambros MB, Reis-Filho JS, Kumar-Sinha C, Chinnaiyan AM. Functionally recurrent rearrangements of the MAST kinase and Notch gene families in breast cancer. *Nat Med* 2011;17:1646-51.
 107. Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Penas PF, Nghiem P. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *J Am Acad Dermatol* 2008;58:375-81.
 108. Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. *J Cutan Pathol* 2010;37:20-7.
 109. Miller NJ, Bhatia S, Parvathaneni U, Iyer JG, Nghiem P. Emerging and mechanism-based therapies for recurrent or metastatic Merkel cell carcinoma. *Curr Treat Options Oncol* 2013;14:249-63.
 110. Samimi M, Touze A. Merkel cell carcinoma: The first human cancer shown to be associated with a polyomavirus. *Presse Med* 2014;43:e405-11.
 111. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 2008;319:1096-100.
 112. Shuda M, Feng H, Kwun HJ, Rosen ST, Gjoerup O, Moore PS, Chang Y. T antigen mutations are a human tumor-specific signature for Merkel cell polyomavirus. *Proc Natl Acad Sci U S A* 2008;105:16272-7.
 113. Shuda M, Kwun HJ, Feng H, Chang Y, Moore PS. Human Merkel cell polyomavirus small T antigen is an oncoprotein targeting the 4E-BP1 translation regulator. *J Clin Invest* 2011;121:3623-34.
 114. Goh G, Walradt T, Markarov V, Blom A, Riaz N, Doumani R, Stafstrom K, Moshiri A, Yelistratova L, Levinsohn J, Chan TA, Nghiem P, Lifton RP, Choi J. Mutational landscape of MCPyV-positive and MCPyV-negative Merkel cell carcinomas with implications for immunotherapy. *Oncotarget* 2016;7:3403-15.
 115. Harms PW, Vats P, Verhaegen ME, Robinson DR, Wu YM, Dhanasekaran SM, Palanisamy N, Siddiqui J, Cao X, Su F, Wang R, Xiao H, Kunju LP, Mehra R, Tomlins SA, Fullen DR, Bichakjian CK, Johnson TM, Dlugosz AA, Chinnaiyan AM. The Distinctive Mutational Spectra of Polyomavirus-Negative Merkel Cell Carcinoma. *Cancer Res* 2015;75:3720-7.
 116. Lemos BD, Storer BE, Iyer JG, Phillips JL, Bichakjian CK, Fang LC, Johnson TM, Liegeois-Kwon NJ, Otley CC, Paulson KG, Ross MI, Yu SS, Zeitouni NC, Byrd DR, Sondak VK, Gershenwald JE, Sober AJ, Nghiem P. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. *J Am Acad Dermatol* 2010;63:751-61.
 117. Lemos B, Nghiem P. Merkel cell carcinoma: more deaths but still no pathway to blame. *J Invest Dermatol* 2007;127:2100-3.
 118. Mauzo SH, Ferrarotto R, Bell D, Torres-Cabala CA, Tetzlaff MT, Prieto VG, Aung PP. Molecular characteristics and potential therapeutic targets in Merkel cell carcinoma. *J Clin Pathol* 2016;69:382-90.
 119. Iyer JG, Parvathaneni U, Gooley T, Miller NJ, Markowitz E, Blom A, Lewis CW, Doumani RF, Parvathaneni K, Anderson A, Bestick A, Liao J, Kane G, Bhatia S, Paulson K, Nghiem P. Single-fraction radiation therapy in patients with metastatic Merkel cell carcinoma. *Cancer Med* 2015;4:1161-70.
 120. Lebbe C, Becker JC, Grob JJ, Malvehy J, Del Marmol V, Pehamberger H, Peris K, Saiag P, Middleton MR, Bastholt L, Testori A, Stratigos A, Garbe C, European Dermatology Forum tEAO-D-O, the European Organization for R, Treatment of C. Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline. *Eur J Cancer* 2015;51:2396-403.
 121. Poulsen M, Rischin D, Walpole E, Harvey J, Mackintosh J, Ainslie J, Hamilton C, Keller J, Tripeony L, Trans-Tasman Radiation Oncology G. High-risk Merkel cell carcinoma of the skin treated with synchronous carboplatin/etoposide and radiation: a Trans-Tasman Radiation Oncology Group Study -- TROG 96.07. *J Clin Oncol* 2003;21:4371-6.
 122. Tai PT, Yu E, Winquist E, Hammond A, Stitt L, Tonita J, Gilchrist J. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. *J Clin Oncol* 2000;18:2493-9.
 123. Fakiha M, Letertre P, Vuillez JP, Lebeau J. Remission of Merkel cell tumor after somatostatin analog treatment. *J Cancer Res Ther* 2010;6:382-4.
 124. Gardair C, Samimi M, Touze A, Coursaget P, Lorette G, Caille A, Wierzbicka E, Croue A, Avenel-Audran M, Aubin F, Kerdraon R, Esteve E, Beneton N, Guyetant S. Somatostatin receptors 2A and 5 are expressed in Merkel cell carcinoma with no association with disease severity. *Neuroendocrinology* 2015;101:223-35.
 125. Davids MS, Charlton A, Ng SS, Chong ML, Laubscher K, Dar M,

- Hodge J, Soong R, Goh BC. Response to a novel multitargeted tyrosine kinase inhibitor pazopanib in metastatic Merkel cell carcinoma. *J Clin Oncol* 2009;27:e97-100.
126. Hafner C, Houben R, Baeurle A, Ritter C, Schrama D, Landthaler M, Becker JC. Activation of the PI3K/AKT pathway in Merkel cell carcinoma. *PLoS One* 2012;7:e31255.
127. Nardi V, Song Y, Santamaria-Barria JA, Cospser 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, Iafate AJ, Cusack JC, Engelman JA, Dias-Santagata D. Activation of PI3K signaling in Merkel cell carcinoma. *Clin Cancer Res* 2012;18:1227-36.
128. Samimi M, Touze A, Laude H, Le Bidre E, Arnold F, Carpentier A, Gardair C, Carlotti A, Maubec E, Dupin N, Aubin F, Avril MF, Rozenberg F, Avenel-Audran M, Guyetant S, Lorette G, Machel L, Coursaget P. Vitamin D deficiency is associated with greater tumor size and poorer outcome in Merkel cell carcinoma patients. *J Eur Acad Dermatol Venereol* 2014;28:298-308.
129. Batinica M, Akgul B, Silling S, Mauch C, Zigrino P. Correlation of Merkel cell polyomavirus positivity with PDGFRalpha mutations and survivin expression in Merkel cell carcinoma. *J Dermatol Sci* 2015;79:43-9.
130. Tolcher AW, Mita A, Lewis LD, Garrett CR, Till E, Daud AI, Patnaik A, Papadopoulos K, Takimoto C, Bartels P, Keating A, Antonia S. Phase I and pharmacokinetic study of YM155, a small-molecule inhibitor of survivin. *J Clin Oncol* 2008;26:5198-203.
131. Lipson EJ, Vincent JG, Loyo M, Kagohara LT, Lubers BS, Wang H, Xu H, Nayyar SK, Wang TS, Sidransky D, Anders RA, Topalian SL, Taube JM. PD-L1 expression in the Merkel cell carcinoma microenvironment: association with inflammation, Merkel cell polyomavirus and overall survival. *Cancer Immunol Res* 2013;1:54-63.
132. Whiteman KR, Johnson HA, Mayo MF, Audette CA, Carrigan CN, LaBelle A, Zukerberg L, Lambert JM, Lutz RJ. Lorvotuzumab mertansine, a CD56-targeting antibody-drug conjugate with potent antitumor activity against small cell lung cancer in human xenograft models. *MAbs* 2014;6:556-66.
133. Vejta T, Sarhadi VK, Koljonen V, Bohling T, Knuutila S. Hotspot mutations in polyomavirus positive and negative Merkel cell carcinomas. *Cancer Genet* 2016;209:30-5.
134. Cohen PR, Tomson BN, Elkin SK, Marchlik E, Carter JL, Kurzrock R. Genomic portfolio of Merkel cell carcinoma as determined by comprehensive genomic profiling: implications for targeted therapeutics. *Oncotarget* 2016;10:18632/ncotarget.8032.
135. Cimino PJ, Robirds DH, Tripp SR, Pfeifer JD, Abel HJ, Duncavage EJ. Retinoblastoma gene mutations detected by whole exome sequencing of Merkel cell carcinoma. *Mod Pathol* 2014;27:1073-87.
136. Graves CA, Jones A, Reynolds J, Stuart J, Pirisi L, Botrous P, Wells J. Neuroendocrine Merkel cell carcinoma is associated with mutations in key DNA repair, epigenetic and apoptosis pathways: a case-based study using targeted massively parallel sequencing. *Neuroendocrinology* 2015;101:112-9.
137. Harms PW, Collie AM, Hovelson DH, Cani AK, Verhaegen ME, Patel RM, Fullen DR, Omata K, Dlugosz AA, Tomlins SA, Billings SD. Next generation sequencing of Cytokeratin 20-negative Merkel cell carcinoma reveals ultraviolet-signature mutations and recurrent TP53 and RB1 inactivation. *Mod Pathol* 2016;29:240-8.
138. Tilling T, Moll I. Which are the cells of origin in merkel cell carcinoma? *J Skin Cancer* 2012;2012:680410.
139. McCardle TW, Sondak VK, Zager J, Messina JL. Merkel cell carcinoma: pathologic findings and prognostic factors. *Curr Probl Cancer* 2010;34:47-64.
140. Zur Hausen A, Rennspiess D, Winnepeninckx V, Speel EJ, Kurz AK. Early B-cell differentiation in Merkel cell carcinomas: clues to cellular ancestry. *Cancer Res* 2013;73:4982-7.
141. Abraham KJ, Zhang X, Vidal R, Pare GC, Feilotter HE, Tron VA. Roles for miR-375 in neuroendocrine differentiation and tumor suppression via Notch pathway suppression in Merkel cell carcinoma. *Am J Pathol* 2016;10.1016/j.ajpath.2015.11.020.
142. Panelos J, Batistatou A, Paglierani M, Zioga A, Maio V, Santi R, Pimpinelli N, De Giorgi V, Santucci M, Massi D. Expression of Notch-1 and alteration of the E-cadherin/beta-catenin cell adhesion complex are observed in primary cutaneous neuroendocrine carcinoma (Merkel cell carcinoma). *Mod Pathol* 2009;22:959-68.
143. Viola D, Valerio L, Molinaro E, Agate L, Bottici V, Biagini A, Lorusso L, Cappagli V, Pieruzzi L, Giani C, Sabini E, Passannati P, Puleo L, Matrone A, Pontillo-Contillo B, Battaglia V, Mazzeo S, Vitti P, Elisei R. Treatment of advanced thyroid cancer with targeted therapies: ten years of experience. *Endocr Relat Cancer* 2016;23:R185-205.
144. Elisei R, Pinchera A. Advances in the follow-up of differentiated or medullary thyroid cancer. *Nat Rev Endocrinol* 2012;8:466-75.
145. Donis-Keller H, Dou S, Chi D, Carlson KM, Toshima K, Lairmore TC, Howe JR, Moley JF, Goodfellow P, Wells SA, Jr. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. *Hum Mol Genet* 1993;2:851-6.
146. Mulligan LM, Kwok JB, Healey CS, Elsdon MJ, Eng C, Gardner E, Love DR, Mole SE, Moore JK, Papi L, Ponder MA, Telenius H, Tunnacliffe A, Ponder BAJ. Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. *Nature* 1993;363:458-60.
147. Ciampi R, Mian C, Fugazzola L, Cosci B, Romei C, Barollo S, Cirello V, Bottici V, Marconcini G, Rosa PM, Borrello MG, Basolo F, Ugolini C, Materazzi G, Pinchera A, Elisei R. Evidence of a low prevalence of RAS mutations in a large medullary thyroid cancer series. *Thyroid* 2013;23:50-7.
148. Agrawal N, Jiao Y, Sausen M, Leary R, Bettgeowda C, Roberts NJ, Bhan S, Ho AS, Khan Z, Bishop J, Westra WH, Wood LD, Hruban RH, Tufano RP, Robinson B, Dralle H, Toledo SP, Toledo RA, Morris LG, Ghossein RA, Fagin JA, Chan TA, Velculescu VE, Vogelstein B, Kinzler KW, Papadopoulos N, Nelkin BD, Ball DW. Exomic sequencing of medullary thyroid cancer reveals dominant and mutually exclusive oncogenic mutations in RET and RAS. *J Clin Endocrinol Metab* 2013;98:E364-9.
149. Schneider TC, de Wit D, Links TP, van Erp NP, van der Hoeven JJ, Gelderblom H, van Wezel T, van Eijk R, Morreau H, Guchelaar HJ, Kapiteijn E. Beneficial Effects of the mTOR Inhibitor Everolimus in Patients with Advanced Medullary Thyroid Carcinoma: Subgroup Results of a Phase II Trial. *Int J Endocrinol* 2015;2015:348124.
150. Lim SM, Chang H, Yoon MJ, Hong YK, Kim H, Chung WY, Park CS, Nam KH, Kang SW, Kim MK, Kim SB, Lee SH, Kim HG, Na, II, Kim YS, Choi MY, Kim JG, Park KU, Yun HJ, Kim JH, Cho BC. A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes. *Ann Oncol* 2013;24:3089-94.
151. Lin SF, Huang YY, Lin JD, Chou TC, Hsueh C, Wong RJ. Utility of a PI3K/mTOR inhibitor (NVP-BEZ235) for thyroid cancer therapy. *PLoS One* 2012;7:e46726.
152. Juweid ME, Hajjar G, Stein R, Sharkey RM, Herskovic T, Swayne LC, Suleiman S, Pereira M, Rubin AD, Goldenberg DM. Initial experience with high-dose radioimmunotherapy of metastatic medullary thyroid cancer using 131I-MN-14 F(ab)2 anti-carcinoembryonic antigen MAb and AHSCR. *J Nucl Med* 2000;41:93-103.
153. Schlumberger MJ, Elisei R, Bastholt L, Wirth LJ, Martins RG, Locati LD, Jarzab B, Pacini F, Daumerie C, Droz JP, Eschenberg MJ, Sun YN, Juan T, Stepan DE, Sherman SI. Phase II study of safety and efficacy of motesanib in patients with progressive or symptomatic, advanced or metastatic medullary thyroid cancer. *J Clin Oncol* 2009;27:3794-801.
154. Locati LD, Licitra L, Agate L, Ou SH, Boucher A, Jarzab B, Qin S, Kane MA, Wirth LJ, Chen C, Kim S, Ingrosso A, Pithavala YK, Bycott P, Cohen EE. Treatment of advanced thyroid cancer with axitinib: Phase 2 study with pharmacokinetic/pharmacodynamic and quality-of-life assessments. *Cancer* 2014;120:2694-703.

155. Wells SA, Jr., Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, Baudin E, Elisei R, Jarzab B, Vasselli JR, Read J, Langmuir P, Ryan AJ, Schlumberger MJ. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012;30:134-41.
156. Elisei R, Schlumberger MJ, Muller SP, Schoffski P, Brose MS, Shah MH, Licitra L, Jarzab B, Medvedev V, Kreissl MC, Niederle B, Cohen EE, Wirth LJ, Ali H, Hessel C, Yaron Y, Ball D, Nelkin B, Sherman SI. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 2013;31:3639-46.
157. Spitzweg C, Morris JC, Bible KC. New drugs for medullary thyroid cancer: new promises? *Endocr Relat Cancer* 2016;10.1530/ERC-16-0104.
158. Cai J, Li L, Ye L, Jiang X, Shen L, Gao Z, Fang W, Huang F, Su T, Zhou Y, Wang W, Ning G. Exome sequencing reveals mutant genes with low penetrance involved in MEN2A-associated tumorigenesis. *Endocr Relat Cancer* 2015;22:23-33.
159. Smith J, Read ML, Hoffman J, Brown R, Bradshaw B, Campbell C, Cole T, Navas JD, Eatock F, Gundara JS, Lian E, McMullan D, Morgan NV, Mulligan L, Morrison PJ, Robledo M, Simpson MA, Smith VE, Stewart S, Trembath RC, Sidhu S, Togneri FS, Wake NC, Wallis Y, Watkinson JC, Maher ER, McCabe CJ, Woodward ER. Germline ESR2 mutation predisposes to medullary thyroid carcinoma and causes up-regulation of RET expression. *Hum Mol Genet* 2016;25:1836-45.
160. Jonsson P, Katchy A, Williams C. Support of a bi-faceted role of estrogen receptor beta (ERbeta) in ERalpha-positive breast cancer cells. *Endocr Relat Cancer* 2014;21:143-60.
161. Horimoto Y, Hartman J, Millour J, Pollock S, Olmos Y, Ho KK, Coombes RC, Poutanen M, Makela SI, El-Bahrawy M, Speirs V, Lam EW. ERbeta1 represses FOXM1 expression through targeting ERalpha to control cell proliferation in breast cancer. *Am J Pathol* 2011;179:1148-56.
162. Williams C, Edvardsson K, Lewandowski SA, Strom A, Gustafsson JA. A genome-wide study of the repressive effects of estrogen receptor beta on estrogen receptor alpha signaling in breast cancer cells. *Oncogene* 2008;27:1019-32.
163. Chang EC, Frasar J, Komm B, Katzenellenbogen BS. Impact of estrogen receptor beta on gene networks regulated by estrogen receptor alpha in breast cancer cells. *Endocrinology* 2006;147:4831-42.
164. Heilmann AM, Subbiah V, Wang K, Sun JX, Elvin JA, Chmielecki J, Sherman SI, Murthy R, Busaidy NL, Subbiah I, Yelensky R, Nangia C, Vergilio JA, Khan SA, Erlich RL, Lipson D, Ross JS, Miller VA, Shah MH, Ali SM, Stephens PJ. Comprehensive genomic profiling of clinically advanced medullary thyroid carcinoma. *Oncology* 2016;90:339-46.
165. Zhu W, Hai T, Ye L, Cote GJ. Medullary thyroid carcinoma cell lines contain a self-renewing CD133+ population that is dependent on ret proto-oncogene activity. *J Clin Endocrinol Metab* 2010;95:439-44.
166. Kucerova L, Feketeova L, Kozovska Z, Poturnajova M, Matuskova M, Nencka R, Babal P. *In vivo* 5FU-exposed human medullary thyroid carcinoma cells contain a chemoresistant CD133+ tumor-initiating cell subset. *Thyroid* 2014;24:520-32.
167. Tang M, Hou YL, Kang QQ, Chen XY, Duan LQ, Shu J, Li SL, Hu XL, Peng ZP. All-trans-retinoic acid promotes iodine uptake via up-regulating the sodium iodide symporter in medullary thyroid cancer stem cells. *Asian Pac J Cancer Prev* 2014;15:1859-62.
168. Bi Y, Meng Y, Wu H, Cui Q, Luo Y, Xue X. Expression of the potential cancer stem cell markers CD133 and CD44 in medullary thyroid carcinoma: A ten-year follow-up and prognostic analysis. *J Surg Oncol* 2016;113:144-51.
169. Stockhausen MT, Sjolund J, Manetopoulos C, Axelson H. Effects of the histone deacetylase inhibitor valproic acid on Notch signalling in human neuroblastoma cells. *Br J Cancer* 2005;92:751-9.
170. Greenblatt DY, Cayo MA, Adler JT, Ning L, Haymart MR, Kunnimalaiyaan M, Chen H. Valproic acid activates Notch1 signaling and induces apoptosis in medullary thyroid cancer cells. *Ann Surg* 2008;247:1036-40.
171. Jaskula-Sztul R, Pisanrturakit P, Landowski M, Chen H, Kunnimalaiyaan M. Expression of the active Notch1 decreases MTC tumor growth *in vivo*. *J Surg Res* 2011;171:23-7.
172. Jaskula-Sztul R, Eide J, Tesfazghi S, Dammalapati A, Harrison AD, Yu XM, Scheinebeck C, Winston-McPherson G, Kupcho KR, Robers MB, Hundal AK, Tang W, Chen H. Tumor-suppressor role of Notch3 in medullary thyroid carcinoma revealed by genetic and pharmacological induction. *Mol Cancer Ther* 2015;14:499-512.
173. Truong M, Cook MR, Pinchot SN, Kunnimalaiyaan M, Chen H. Resveratrol induces Notch2-mediated apoptosis and suppression of neuroendocrine markers in medullary thyroid cancer. *Ann Surg Oncol* 2011;18:1506-11.
174. Tesfazghi S, Eide J, Dammalapati A, Korlesky C, Wyche TP, Bugni TS, Chen H, Jaskula-Sztul R. Thiocoraline alters neuroendocrine phenotype and activates the Notch pathway in MTC-TT cell line. *Cancer Med* 2013;2:734-43.