

Supplemental Information

Polycomb Group Proteins: Multi-Faceted Regulators of Somatic Stem Cells and Cancer

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REFERENCES FOR TABLE 1.

1. Arisan, S., Buyuktuncer, E.D., Palavan-Unsal, N., et al. (2005). Increased expression of EZH2, a polycomb group protein, in bladder carcinoma. *Urol. Int.* 75, 252–257.
2. Bachmann, I.M., Halvorsen, O.J., Collett, K., et al. (2006). EZH2 expression is associated with high proliferation rate and aggressive tumor subgroups in cutaneous melanoma and cancers of the endometrium, prostate, and breast. *J. Clin. Oncol.* 24, 268-273.
3. Beà, S., Tort, F., Pinyol, M., Puig, X., Hernández, L., Hernández, S., Fernandez, P.L., van Lohuizen, M., Colomer, D., and Campo, E. (2001). BMI-1 gene amplification and overexpression in hematological malignancies occur mainly in mantle cell lymphomas. *Cancer Res.* 61, 2409-2412.
4. Boultwood, J., Perry, J., Pellagatti, A., Fernandez-Mercado, M., Fernandez-Santamaria, C., Calasanz, M.J., Larrayoz, M.J., Garcia-Delgado, M., Giagounidis, A., Malcovati, L., et al. (2010). Frequent mutation of the polycomb-associated gene ASXL1 in the myelodysplastic syndromes and in acute myeloid leukemia. *Leukemia* 24, 1062-1065.
5. Bracken, A.P., Pasini, D., Capra, M., Prosperini, E., Colli, E., and Helin, K. (2003). EZH2 is downstream of the pRB-E2F pathway, essential for proliferation and amplified in cancer. *EMBO J.* 22, 5323-5335.
6. Carbuccia, N., Murati, A., Trouplin, V., Brecqueville, M., Adélaïde, J., Rey, J., Vainchenker, W., Bernard, O.A., Chaffanet, M., Vey, N., et al. (2009). Mutations of ASXL1 gene in myeloproliferative neoplasms. *Leukemia* 23, 2183-2186.
7. Carbuccia, N., Trouplin, V., Gelsi-Boyer, V., Murati, A., Rocquain, J., Adélaïde, J., Olschwang, S., Xerri, L., Vey, N., Chaffanet, M., et al. (2010). Mutual exclusion of ASXL1 and NPM1 mutations in a series of acute myeloid leukemias. *Leukemia* 24, 469-473.
8. Collett, K., Eide, G.E., Arnes, J., et al. (2006). Expression of enhancer of zeste homologue 2 is significantly associated with increased tumor cell proliferation and is a marker of aggressive breast cancer. *Clin. Cancer Res.* 12, 1168–1174.
9. Deshpande, A.M., Akunowicz, J.D., Reveles, X.T., Patel, B.B., Saria, E.A., Gorlick, R.G., Naylor, S.L., Leach, R.J., and Hansen, M.F. (2007). PHC3, a component of the hPRC-H complex, associates with E2F6 during G0 and is lost in osteosarcoma tumors. *Oncogene* 26, 1714-1722.
10. Ernst, T., Chase, A.J., Score, J., Hidalgo-Curtis, C.E., Bryant, C., Jones, A.V., Waghorn, K., Zoi, K., Ross, F.M., Reiter, A., et al. (2010). Inactivating mutations of the histone methyltransferase gene EZH2 in myeloid disorders. *Nat. Genet.* 42, 722-726.
11. Gelsi-Boyer, V., Trouplin, V., Adélaïde, J., Bonansea, J., Cervera, N., Carbuccia, N., Lagarde, A., Prebet, T., Nezri, M., Sainty, D., et al. (2009). Mutations of polycomb-

- associated gene ASXL1 in myelodysplastic syndromes and chronic myelomonocytic leukaemia. *Br. J. Haematol.* 145, 788-800.
- 12. Iwata, S., Takenobu, H., Kageyama, H., Koseki, H., Ishii, T., Nakazawa, A., Tatezaki, S., Nakagawara, A., and Kamijo, T. (2010). Polycomb group molecule PHC3 regulates polycomb complex composition and prognosis of osteosarcoma. *Cancer Sci.* 101, 1646-1652.
 - 13. Karamitopoulou, E., Pallante, P., Zlobec, I., Tornillo, L., Carafa, V., Schaffner, T., et al. (2010). Loss of the CBX7 protein expression correlates with a more aggressive phenotype in pancreatic cancer. *Eur. J. Cancer*, 46, 1438-1444.
 - 14. Kirmizis, A., Bartley, S.M., and Farnham, P.J. (2003). Identification of the polycomb group protein SU(Z)12 as a potential molecular target for human cancer therapy. *Mol. Cancer Ther.* 2, 113-121.
 - 15. Kleer, C.G., Cao, Q., Varambally, S., et al. (2003). EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells. *Proc. Natl. Acad. Sci. USA* 100, 11606–11611.
 - 16. Koontz, J.I., Soreng, A.L., Nucci, M., et al. (2001). Frequent fusion of the JAZF1 and JJAZ1 genes in endometrial stromal tumors. *Proc. Natl. Acad. Sci. USA* 98, 6348-6353.
 - 17. Krzellock, R.P., Murphy, E.C., Strong, L.C., Naylor, S.L., and Hansen, M.F. (1997). Localization of a novel tumor suppressor locus on human chromosome 3q important in osteosarcoma tumorigenesis. *Cancer Res.* 57, 106-109.
 - 18. Leung, C., Lingbeek, M., Shakhova, O., et al. (2004). Bmi1 is essential for cerebellar development and is overexpressed in human medulloblastomas. *Nature* 428, 337-341.
 - 19. Li, H., Ma, X., Wang, J., Koontz, J., Nucci, M., and Sklar, J. (2007). Effects of rearrangement and allelic exclusion of JJAZ1/SUZ12 on cell proliferation and survival. *Proc. Natl. Acad. Sci. USA* 104, 20001-20006.
 - 20. Martín-Pérez, D., Sánchez, E., Maestre, L., Suela, J., Vargiu, P., Di Lisio, L., Martínez, N., Alves, J., Piris, M.A., and Sánchez-Beato, M. (2010). Deregulated expression of the polycomb-group protein SUZ12 target genes characterizes mantle cell lymphoma. *Am. J. Pathol. Epub ahead of print.*
 - 21. Micci, F., Panagopoulos, I., Bjerkehagen, B., and Heim, S. (2006). Consistent rearrangement of chromosomal band 6p21 with generation of fusion genes JAZF1/PHF1 and EPC1/PHF1 in endometrial stromal sarcoma. *Cancer Res.* 66, 107-112.
 - 22. Mimori, K., Ogawa, K., Okamoto, M., et al. (2005). Clinical significance of enhancer of zeste homolog 2 expression in colorectal cancer cases. *Eur. J. Surg. Oncol.* 31, 376–380.
 - 23. Morin, R.D., Johnson, N.A., Severson, T.M., Mungall, A.J., An, J., Goya, R., Paul, J.E., Boyle, M., Woolcock, B.W., Kuchenbauer, F., et al. (2010). Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. *Nat. Genet.* 42, 181-185.
 - 24. Nakahata, S., Saito, Y., Hamasaki, M., Hidaka, T., Arai, Y., Taki, T., Taniwaki, M., and Morishita, K. (2009). Alteration of enhancer of polycomb 1 at 10p11.2 is one of the genetic events leading to development of adult T-cell leukemia/lymphoma. *Genes Chromosomes Cancer* 48, 768-776.
 - 25. Nikoloski, G., Langemeijer, S.M., Kuiper, R.P., Knops, R., Massop, M., Tönnissen, E.R., van der Heijden, A., Scheele, T.N., Vandenberghe, P., de Witte, T., et al. (2010). Somatic mutations of the histone methyltransferase gene EZH2 in myelodysplastic syndromes. *Nat. Genet.* 42, 665-667.

26. Nowak, K., Kerl, K., Fehr, D., et al. (2006). BMI1 is a target gene of E2F-1 and is strongly expressed in primary neuroblastomas. *Nucleic Acids Res.* 34, 1745-1754.
27. Raaphorst, F. M. et al. (2003). Poorly differentiated breast carcinoma is associated with increased expression of the human Polycomb group EZH2 gene. *Neoplasia* 5, 481-488.
28. Raaphorst, F.M., van Kemenade, F.J., Blokzijl, T., et al. (2000). Coexpression of BMI-1 and EZH2 polycomb group genes in Reed-Sternberg cells of Hodgkin's disease. *Am. J. Pathol.* 157, 709-715.
29. Raman, J.D., Mongan, N.P., Tickoo, S.K., Boorjian, S.A., Scherr, D.S., and Gudas, L.J. (2005). Increased expression of the polycomb group gene, EZH2, in transitional cell carcinoma of the bladder. *Clin. Cancer Res.* 11, 8570-8576.
30. Sanchez-Beato, M., Sanchez, E., Gonzalez-Carrero, J., et al. (2006). Variability in the expression of polycomb proteins in different normal and tumoral tissues. A pilot study using tissue microarrays. *Mod. Pathol.* 19, 684-694.
31. Sawa, M., Yamamoto, K., Yokozawa, T., et al. (2005). BMI-1 is highly expressed in M0-subtype acute myeloid leukemia. *Int. J. Hematol.* 82, 42-47.
32. Scott, C.L., Gil, J., Hernando, E., et al. (2007). Role of the chromobox protein CBX7 in lymphomagenesis. *Proc. Natl. Acad. Sci. USA* 104, 5389-5394.
33. Sudo, T., Utsunomiya, T., Mimori, K., et al. (2005). Clinicopathological significance of EZH2 mRNA expression in patients with hepatocellular carcinoma. *Br. J. Cancer* 92, 1754-1758.
34. Tokimasa, S., Ohta, H., Sawada, A., et al. (2001). Lack of the Polycomb-group gene rae28 causes maturation arrest at the early B-cell developmental stage. *Exp. Hematol.* 29, 93-103.
35. van Kemenade, F. J. et al. Coexpression of BMI-1 and EZH2 Polycomb-group proteins is associated with cycling cells and degree of malignancy in B-cell non-Hodgkin lymphoma. *Blood* 97, 3896-3901 (2001).
36. Varambally, S., Dhanasekaran, S.M., Zhou, M., et al. (2002). The polycomb group protein EZH2 is involved in progression of prostate cancer. *Nature* 419, 624-629.
37. Visser, H.P., Gunster, M.J., Kluij-Nellemans, H.C., et al. (2001). The Polycomb group protein EZH2 is upregulated in proliferating, cultured human mantle cell lymphoma. *Br. J. Haematol.* 112, 950-958.
38. Vonlanthen, S., Heighway, J., Altermatt, H.J., et al. (2001). The bmi-1 oncogene is differentially expressed in non-small cell lung cancer and correlates with INK4A-ARF locus expression. *Br. J. Cancer* 84, 1372-1376.
39. Wang, S., Robertson, G.P., and Zhu, J. (2004). A novel human homologue of Drosophila polycomblike gene is up-regulated in multiple cancers. *Gene* 343, 69-78.
40. Wang, W., Yuasa, T., Tsuchiya, N., Ma, Z., Maita, S., Narita, S., Kumazawa, T., Inoue, T., Tsuruta, H., Horikawa, Y., et al., (2009). The novel tumor-suppressor Mel-18 in prostate cancer: its functional polymorphism, expression and clinical significance. *Int. J. Cancer* 125, 2836-2843.
41. Weikert, S., Christoph, F., Kollermann, J., et al. (2005). Expression levels of the EZH2 polycomb transcriptional repressor correlate with aggressiveness and invasive potential of bladder carcinomas. *Int. J. Mol. Med.* 16, 349-353.
42. Widschwendter, M., Fiegl, H., Egle, D., et al. (2007). Epigenetic stem cell signature in cancer. *Nat. Genet.* 39, 157-158.