receptor are candidates for treatment with this drug (114). A high percentage of ER-positive breast cancers that respond to initial tamoxifen treatment subsequently develop resistance. Sustained tamoxifen resistance continues to be a major problem in managing advanced breast cancer (115). Miller et al. (116) and Fan et al. (117) describe mechanisms by which estrogen receptor acquires resistance to tamoxifen. These include mutations in the tumor's genome that lead to increased activity of the tumor's phosphatidylinositol 3-kinase (PI3K) and can lead to resistance against tamoxifen. Also, tamoxifen resistance can result from reduced expression of TGF-beta receptor type 2, and from increased expression of ABCG2 multidrug resistance protein (118).

*Imatinib*. c-KIT is a kinase that mediates cell-signaling in normal and cancer cells. But in some tumor cells, c-KIT acquires a mutation that is responsible for the transformation of a normal host cell to a tumor cell (119). Imatinib, which inhibits c-KIT, is used to treat patients with tumors where c-KIT is responsible for this transformation. Mutations in c-KIT that result in drug resistance should be distinguished from mutations in c-KIT that result in the conversion of normal c-KIT into an oncogene (120). Normally, c-KIT is used for erythropoiesis and melanin formation, but mutations can result in this conversion (121). But with imatinib, 50% of patients develop resistance due to additional mutations in c-KIT. Therefore, second-line treatment is with another drug, sunitinib. Sunitinib has been approved for use in cancer, after failure of imatinib due to the tumor's resistance to imatinib (122). Hence, where a clinical study is to be conducted with imatinib, it is reasonable that the Clinical Study Protocol mandate that the subjects be treatment-naive with regard to imatinib, to ensure that the tumors in the subjects are not resistant to imatinib.

[114]Higgins MJ, Stearns V. Understanding resistance to tamoxifen in hormone receptor-positive breast cancer. Clin. Chem. 2009;55:1453–5.

[115]Kumar R, Zhang H, Holm C, Vadlamudi RK, Landberg G, Rayala SK. Extranuclear coactivator signaling confers insensitivity to tamoxifen. Clin. Cancer Res. 2009;15:4123–30.

[116]Miller TW, Pérez-Torres M, Narasanna A, et al. Loss of phosphatase and tensin homologue deleted on chromosome 10 engages ErbB3 and insulin-like growth factor-I receptor signaling to promote antiestrogen resistance in breast cancer. Cancer Res. 2009;69:4192–201.

[117]Fan P, Yue W, Wang JP, et al. Mechanisms of resistance to structurally diverse antiestrogens differ under premenopausal and postmenopausal conditions: evidence from in vitro breast cancer cell models. Endocrinology. 2009;150:2036–45.

[118]Busch S, et al. Loss of TGFbeta receptor type 2 expression impairs estrogen response and confers tamoxifen resistance. Cancer Res. 2015;75:1457–69.

[119]Roberts KG, Smith AM, McDougall F, et al. Essential requirement for PP2A inhibition by the oncogenic receptor c-KIT suggests PP2A reactivation as a strategy to treat c-KIT + cancers. Cancer Res. 2010;70:5438–47.

[120]Bamba S, Hirota S, Inatomi O, et al. Familial and multiple gastrointestinal stromal tumors with fair response to a half-dose of imatinib. Intern. Med. 2015;54:759–64.

[121]Oriss TB, et al. Dendritic cell c-kit signaling and adaptive immunity: implications for the upper airways. Curr. Opin. Allergy Clin. Immunol. 2014;14:7–12.

[122]Gajiwala KS, Wu JC, Christensen J, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proc. Natl. Acad. Sci. USA 2009;106:1542–7.