PI3 Kinase Inhibitors for the Treatment of Cancer

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The superfamily of PI3 kinases is characterized by primary sequence homologies within the catalytic domain of these enzymes. Currently, 8 members of this family are known, belonging to three classes (I-III). At structural level, the enzyme PI3K is composed of a 110-kDa catalytic subunit and an 85-kDa adaptor subunit. PI3K signaling regulates diverse cellular functions, including protein synthesis and glucose metabolism, cell survival and growth, proliferation, cellular resilience and repair, cell migration, and angiogenesis (Katso, et al 2001).

Multiple components of the PI3K pathway are often dysregulated in cancer cells and over-activation of PI3K signaling is implicated in many aspects of tumor growth and survival. Activation of this pathway can be the result of: i) Amplification and/or overexpression of the p110α catalytic subunit; ii) Presence of activating mutations in the PIK3CA gene encoding the p110α catalytic subunit; iii) Constitutively active mutants or overexpression of some receptor tyrosine kinases (e.g. EGFR, ErbB2) leading to constitutive recruitment and activation of PI3K; iv) Constitutive recruitment and activation by mutant forms of the Ras oncogene; v) Loss or inactivating mutation of the tumor suppressor gene PTEN, a endogenous negative regulator of the PI3K pathway; or vi) Overexpression of the downstream kinase Akt.

Preliminary data suggest that activation of the PI3K pathway may be a predictor of poor prognostic outcome in many cancers. Several lines of evidence suggest that inhibition of the PI3K signaling pathway might provide benefit for the treatment of many cancers: solid tumors (breast cancer, prostate cancer, glioblastoma multiforme, colon cancer, lung cancer, etc.) and tumors of the hematopoietic system (Kim 1994, Ram 1996, Ma 2000, Fry 2001, Roymans 2001, Bachman 2004, Broderick 2004, Samuels 2004, Ohgaki 2005, Zeng 2006).

Therapeutic interventions can impact PI3K signaling and the activation of the pathway could contribute to the therapeutic resistance of tumors or could alternatively increase the efficacy of chemotherapy/radiation. Exposure of tumor cells to cytotoxic agents, treatment with trastuzumab or with tamoxifen or letrozole can also lead to constitutive activation of the PI3K pathway (Brognard 2001, Clark 2002, Campbell 2004, Ellis 2004). In the case of trastuzumab/lapatinib treatment, preliminary evidence suggested that activation of the PI3K signaling pathway may play a role in the development of resistance (Fujita 2006, Nahta 2006a, Nahta 2006b, Dieras 2007). For example, PTEN activation is important for the growth inhibitory effect of trastuzumab, whereas loss of PTEN function is predictive of trastuzumab and gefitinib resistance (Nagata 2004, She 2005). Together these insights suggest that many cancers, either treatment naïve or following exposure to anti-cancer treatment, exhibit a 'genetic dependency' to PI3K pathway activation, which can be exploited for biomarker guided therapeutic gain from PI3K inhibition.