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Tegatrabetan (BC-2059) – A new approach to targeting beta catenin and Wnt activation

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We are developing Tegatrabetan (BC-2059), a novel small molecule targeting the WNT/beta catenin pathway. The WNT/beta catenin pathway is mutated and/or activated in a large number of different tumor types. A large fraction of Desmoid tumors have been found to contain activating mutations in the beta catenin protein causing dysregulated transcriptional activity. Tegatrabetan disrupts the interaction between beta catenin and the transcriptional cofactor TBL1 (Transducin Beta Like Protein 1) resulting in the degradation of beta catenin and the inhibition of WNT pathway transcriptional activity. It is a potent inhibitor of cancer cell growth (1-300nM GI50) and invasion, and induces both cell cycle arrest and cell death.

TBL1 family members (TBLX1 and TBLXR1), under Wnt stimulation are post-translationally modified, inducing a conformational shift to a high affinity binding partner for beta catenin. The beta catenin/TBL1 complex protects the beta catenin protein from degradation, and is required to form an active transcriptional unit. Tegatrabetan interacts with TBL1, disrupts TBL1/beta catenin binding, freeing beta catenin from the transcription complex which allows it to be degraded by the normal proteasomal cellular machinery. Preclinical animal studies have found that Tegatrabetan is well tolerated with high blood levels achievable with no significant toxicity. The compound is able to decrease Beta catenin protein levels in both tumor and surrogate tissues, and is active in animal models of Acute Myeloid Leukemia and Multiple Myeloma resulting in significant increases in survival over control treated animals.

The mechanism of Tegatrabetan, which targets the WNT/beta catenin pathway at the transcriptional complex, has therapeutic potential in diseases with mutations in beta catenin such as Desmoid malignancies.