**Supplementary Tables**

**Suppl. Table 1. Binding mode of Debio 0617B to ABL.**

Kd were determined in duplicate in phosphorylated and non-phosphorylated forms of ABL kinase. The active site binding of type I inhibitors typically are not sensitive to phosphorylation of the activation loop, thus there should be little to no offset in Kd measurements between phosphorylated and non-phosphorylated versions of ABL1 in this system. A compound displaying a type II inhibitor binding would show strong offsets in Kd measurements (at least 10-fold preference for non-phosphorylated) for most, if not the entire, suite of ABL1 activation state specific assay pairs. The modest Kd offset (~7-fold) observed for one assay pair (ABL1(T315I)) is the sole outlier; however, this is not uncommon as some type I inhibitors can show similar small offsets for a subset of the assay pairs tested (38).

**Suppl. Table 2. Physico-chemical and early ADME profile of Debio 0617B.**

**Suppl. Table 3. Debio 0617B activity on a panel of 21 cancer cell lines.**

Cells were seeded in 96-well plates and treated in triplicate with increasing concentrations of Debio 0617B for 72 h. Colorimetric MTT assays were performed, and absorbance was measured at 570 nm. Percent growth rates were calculated relative to untreated control, and curve fit analysis was performed to determine the IC50 concentrations (in µM; avg. R2 value=0.97). Relative sensitivity is described here.

**Suppl. Table 4.** **PK/PD Profile of Debio 0617B in mice with A549 tumors.**