

## **BTM-3528 Potently Induces G0/G1 Cell Cycle Arrest and is Efficacious in Preclinical Models of Diffuse Large B Cell Lymphoma (DLBCL)**

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Aberrant regulation of cell cycle control, integration of signals from oncogenic signaling pathways, and cancer cell metabolism play a key role in the pathogenesis of multiple hematologic malignancies and solid tumors. BTM-3528 is an orally available compound that causes concentration dependent cell cycle arrest in the G0/G1 phase of the cell cycle, rapidly decreases cellular glutathione levels and induces expression of p21. BTM-3528 has no significant biochemical activity against a panel of known drug targets including kinases (in addition to cyclin dependent kinases), G-protein coupled receptors, ion channels, and histone deacetylases. For the described study, the activity of BTM-3528 was evaluated in *in vitro* and *in vivo* models of diffuse large B cell lymphoma (DLBCL).

Profiling of BTM-3528 across a panel of hematologic and solid tumor cancer cell lines demonstrated potent anti-proliferative activity against a select set of cancer cell types without effect on normal human cells. These included multiple DLBCL cell lines notably of germinal center B cell (GCB) subtype. The majority of the DLBCL cell lines tested were characterized by *Myc* and *Bcl-2* gene rearrangements or amplifications. Cell proliferation was 100% inhibited with IC50s ranging from 0.14 to 0.52  $\mu$ M in these DLBCL cell lines. Furthermore, at these concentrations apoptosis was induced in these cell lines by BTM-3528. In the context of G0/G1 cell cycle arrest, BTM-3528 decreased Cyclin D3 and *Myc* protein expression.

*In vivo* pharmacokinetic studies showed that BTM-3528 has excellent oral bioavailability with a murine  $t_{1/2}$  of 6 hours. BTM-3528 was tested in a human subcutaneous DLBCL xenograft model (BJAB). Post tumor implants, animals with tumors  $> 250 \text{ mm}^3$ , were dosed once daily with BTM-3528 at the maximum tolerated dose of QD 75 mg/kg orally for 14 days. Significant anti-tumor activity was observed by day 3 of treatment with prompt and sustained tumor regressions. Furthermore, following discontinuation of BTM-3528 after 14 days of treatment, sustained complete tumor regressions were maintained in 50% of the treated animals.

Preliminary toxicology evaluation of BTM-3528 showed no adverse effect on hematopoiesis or hepatic function.

**Conclusion:** BTM-3528 is a novel orally bioavailable compound with a unique mechanism of action based on G1/G0 cell cycle arrest and modulation of cancer cell metabolism. It shows significant activity and a favorable toxicity profile in *in vitro* and *in vivo* models of DLBCL. These results underscore the clinical development potential of BTM-3528 for the treatment of DLBCL.