TPS7097: A Phase 1 Trial of BTM-3566 in Relapsed/Refractory Mature B Cell Lymphomas

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BANTAM PHARMACEUTICAL

Background

Relapsed or refractory (r/r) mature B-cell lymphomas remain a substantial unmet clinical need, marked by disease recurrence or primary resistance of lymphoma after initial treatment. The pathogenesis of r/r mature B-cell lymphomas involves complex molecular alterations, including mutations in key signaling pathways, immune evasion mechanisms, and microenvironmental factors that contribute to resistance. Despite advancements in chemotherapy, immunotherapy, targeted therapy, CAR T-cell therapy and bispecific antibodies, a substantial proportion of patients relapse or fail to respond to treatment. What is urgently needed are therapies that lead to robust and durable disease regression independent of tumor genotype or target expression. In addition, the toxicities associated with r/r B-cell lymphoma treatment remain significant and often result in prolonged cytopenias which prevent safe administration of additional therapies. Consequently, there remains an urgent need for novel therapeutic approaches that can be effectively utilized in patients with neutropenia and/or thrombocytopenia while improving patient outcomes.

BTM-3566: A Novel Therapeutic Approach

BTM-3566 is a first-in-class, orally delivered small molecule that specifically activates the mitochondrial protease, OMA1 leading to cell death in numerous malignancies. **See Figure 1.** This pathway links mitochondrial OMA1 activation to the integrated stress response (ISR) and regulation of apoptotic signaling. In preclinical studies, BTM-3566 led to rapid apoptosis in numerous hematologic tumor cell lines, with deepest responses observed in those derived from Diffuse Large B-cell (including double and triple-hit sub-types), Mantle Cell, Burkitt's and Follicular, with most lines exhibiting >85% growth inhibition and cell death. The anti-tumor effect is independent of genotype as double and triple hit DLBCL are responsive. *In vivo*, BTM-3566 induces complete and durable regression in xenograft models of human DLBCL and MCL. Importantly, no regrowth is seen through 21 days post therapy. In an expanded panel of high-risk human DLBCL PDX models BTM-3566 demonstrated a 100% response rate, and complete tumor regression in 6 of 9 PDX models. The mechanistic dependence of BTM-3566 on low FAM210B levels in tumors was demonstrated in nonclinical studies of lymphomas, as nearly all lymphomas feature low FAM210B expression levels. This observation supported further studies of BTM-3566 in solid tumors, whose data also demonstrated tumor regressions in PDX models of uterine and esophageal tumors, as well as substantial growth inhibition in other tumor types expressing low levels of FAM210B. These findings support exploring BTM-3566 therapeutic applications beyond lymphomas. IND enabling safety studies indicate drug treatment is well tolerated and does not lead to cytopenias, neuropathies or neurotoxicity.

Mechanism of Action

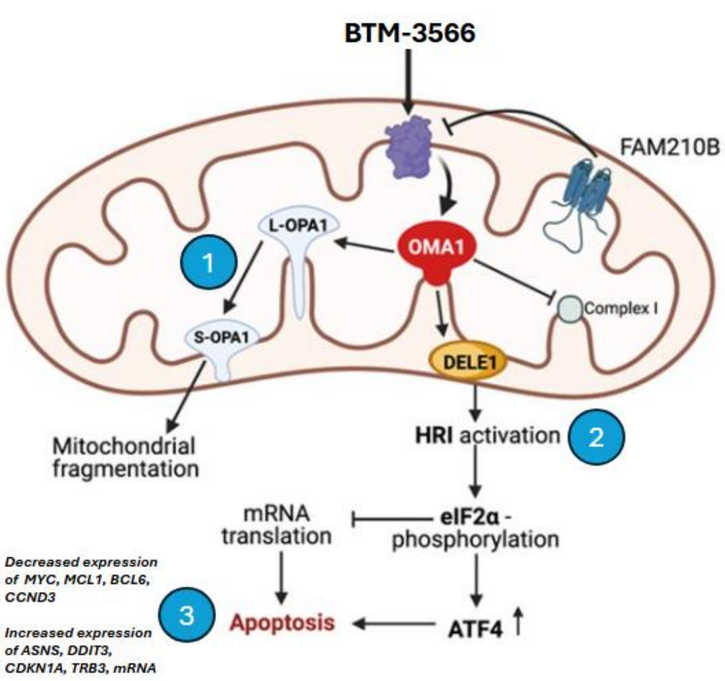

Figure 1: Model for the mechanism of action of BTM compounds. BTM compounds induce the activation of OMA1 leading to the cleavage of DELE1 and OPA1. (1) OPA1 activation leads to fragmentation of the mitochondrial network. (2) DELE1 cleavage leads to activation of HRI and (3) a reduction in pro-survival factors and downstream ATF4-ISR effector pathways leading to cell death in DLBCL cell lines.

Study Design

BTM-3566-001 is a multi-center, prospective, single-arm, phase 1 dose escalation and expansion study currently enrolling in the United States. The dose escalation phase of the study will include patients with any sub-type of relapsed/refractory mature B-cell lymphomas. Patients will be enrolled using a 3+3 design with a starting dose of 0.3 mg/kg. A modified Fibonacci sequence will be utilized to escalate to a pharmacologically optimal dose or a maximum tolerated dose. **See Figure 2.**

BTM-3566-001-CA is a nearly identical Canadian sub-protocol of the BTM-3566-001 study which differs only in starting dose and escalation design. In Canada, single patient cohorts will be initiated at a starting dose of 0.9 mg/kg and escalation will be in 33% increments (0.9, 1.2, 1.7, 2.2, etc.). When a patient in a single-patient cohort experiences one grade ≥2 treatment related toxicity lasting for more than 72 hours or two grade ≥2 treatment related toxicities (regardless of duration), the cohort will be expanded and the 3+3 design implemented for the remainder of dose escalation.

In both studies, patients will be dosed on Days 1 through 7 of a 14-day cycle and will continue treatment until disease progression, occurrence of a treatment-related Grade ≥4 adverse event, withdrawal of consent, or other protocol-specified reason. The dose-limiting toxicity (DLT) period will consist of the first 2 treatment cycles (Day 1 to Day 18).

The safety review committee will convene after each dose-level cohort is complete. The dose level will be cleared, and patients will be enrolled into the next highest dose level of BTM-3566 if 0/3 (or 1/6 patients) experiences a DLT. Once a dose level has been cleared, patients enrolled at lower dose levels will be permitted to escalate to the cleared dose after discussion with the local investigator and study medical monitor.

Upon completion of the dose escalation phase of the study, the dose expansion phase of the study will be initiated in select subtypes of mature B-cell lymphomas, such as Diffuse Large B-cell Lymphoma (DLBCL), Mantle Cell Lymphoma (MCL), Burkitt's Lymphoma (BL) or Follicular Lymphoma (FL).

Dose Escalation Schema

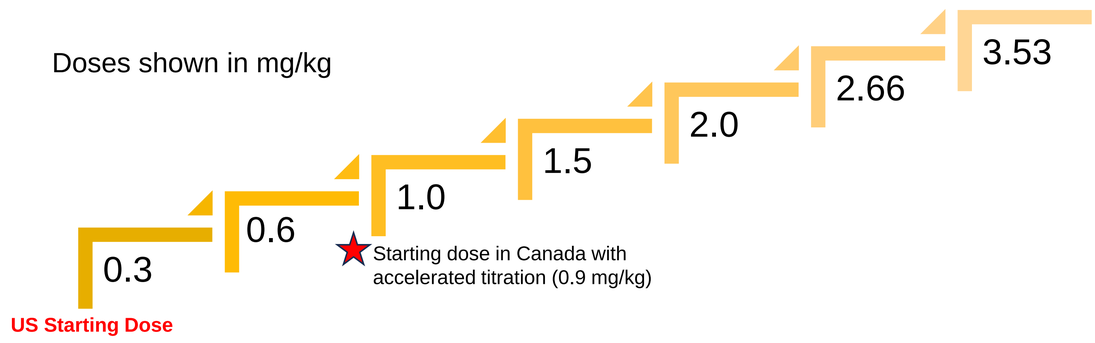

Figure 2: US Dose Escalation Design Using a starting dose of 0.3mg/kg, patients will be dosed in 3+3 dose level cohorts with escalation using a modified Fibonacci design until a pharmacologically optimal or maximum tolerated dose is reached.

Endpoints

Primary:
- Evaluate the safety of therapy with BTM-3566 defined as rates of dose limiting toxicities and adverse events
- Determine the recommended phase 2 dose

Secondary:
- Determine the pharmacokinetic properties of BTM-3566
- Evaluate the clinical activity of BTM-3566 through objective response rates per Revised Lugano classification

Exploratory:
- Evaluate additional measures of clinical activity such as duration of response, disease control rate, progression-free and overall survival
- Evaluate changes in circulating tumor DNA from baseline to on-therapy
- Evaluate potential pharmacodynamic biomarkers of BTM-3566 modulation of downstream pathways in peripheral or surrogate tissues
- Evaluate candidate predictive biomarkers of BTM-3566 clinical response in tissue specimens and germline DNA
- Evaluate histologic changes within diseased lymph node(s) from pre-treatment to on-treatment, including biomarker analysis of mechanism-based effects and evidence of cell death

Key Inclusion Criteria

- Adult patients ≥ 18 years of age with a diagnosis of relapsed or refractory mature B-cell lymphoma
- Patients with Non-Hodgkins lymphoma must have received 2 or more prior lines of therapy and have no available therapies with known clinical benefit
- Must have measurable disease per response evaluation criteria in lymphoma (Lugano classification)
- Eastern Cooperative Oncology Group performance status of 0 to 2
- Have a life expectancy of ≥ 3 months
- Have adequate organ function as demonstrated in protocol-specified laboratory values, including but not limited to:
  - Hemoglobin ≥ 8.0g/dL
  - Absolute neutrophil count ≥ 1.0 x 109 cells/L
  - AST and ALT ≤ 2.5 x ULN (or ≤ 5 x ULN if liver involvement)
  - Creatinine < 1.5 x ULN or CrCl ≥ 60 mL/min
  - cTnI < 99% ULN per local assay
  - Platelets ≥ 75 x 109 cells/L
  - Total bilirubin ≤ 1.5 x ULN
  - Creatinine Kinase < ULN
  - QTc < 470 ms for females and < 450 for males
  - NT-proBNP < age-adjusted “rule in” value for CHG
  - Left Ventricular Ejection Fraction (LVEF) ≥ 50% or ≥ LLN for the institution, whichever is higher
- Have a site of disease amenable to biopsy and be a candidate for tumor biopsy according to institutional guidelines
- Must agree to use adequate birth control throughout the study and for 90 days following the last dose of BTM-3566
- Must be willing to adhere to the study visit schedule and the prohibitions and restrictions specified in the protocol

Key Exclusion Criteria

- Has ongoing toxicity ≥ Grade 1 from prior therapy (with exception of alopecia, vitiligo, Gr 1/2 neuropathy, and well-controlled endocrinopathies)
- Had major surgery within 3 months of first dose of BTM-3566
- Received any anti-cancer therapy (including radiation of curative intent) within 28 days of first dose of BTM-3566
- Has primary CNS lymphoma
- Cannot avoid drugs that prolong the QT interval from 7 days prior to the first dose of study drug and throughout the study
- Has a history (within 6 months of study entry) of NYHA Grade ≥ 2 CHF, unstable angina, myocardial infarction, uncontrolled HTN or other serious cardiac conditions
- Has history of statin-associated myopathy within 6 months of study start and is still taking a statin
- Has previously received a total anthracycline dose ≥ 360 mg/m^2 doxorubicin or equivalent
- Requires prolonged use of a moderate or strong CYP3A4 inhibitors or inducers
- Has symptomatic or uncontrolled neurologic disease not definitively treated with surgery or radiation
- Has a second malignancy at other sites
- Has active and clinically significant bacterial, fungal or viral infection
- Women who are pregnant or breast feeding

References and Acknowledgements

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