Trial in Progress: Phase 1 Study of BXCL701, a Dipeptidyl Peptidase Inhibitor, in Relapsed/Refractory Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome

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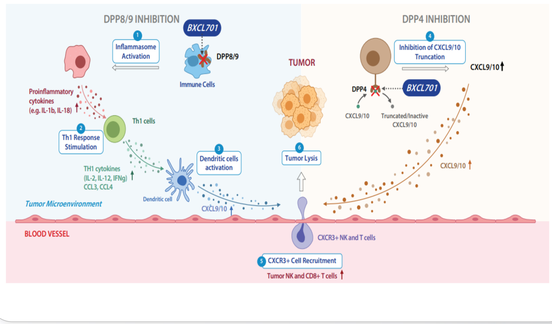
INTRODUCTION

Novel therapies in AML either targeting small molecules or apoptotic proteins have markedly improved AML responses, however the overall prognosis is still poor. Novel treatments are needed for this deadly disease.

BXCL701

- BXCL701 (talabostat, formerly PT-100) is an oral innate immune activator and a competitive inhibitor of dipeptidyl peptidases (DPP) primarily DPP8/9, and DPP4
- Studied in patients with mCRPC of adenocarcinoma and SCNC phenotypes, NSCLC, metastatic melanoma, pancreatic cancer and advanced CLL and NHL

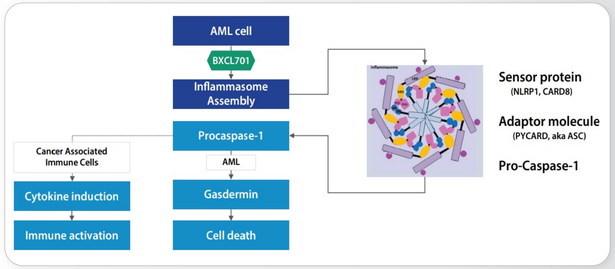
BXCL701 MECHANISM OF ACTION



DPP inhibition results into antitumor immune response through 2 mechanisms in solid tumors

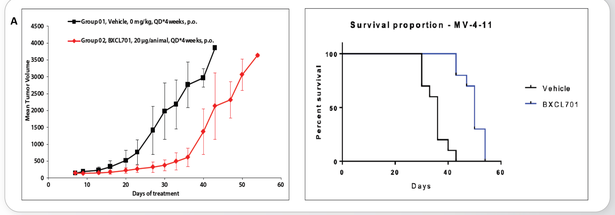
1. DPP8/9 inhibition activates inflammasome leading to immune cell pyroptosis and increased proinflammatory cytokines, stimulation of Th1 response, and dendritic cell activation via CXCL9/10-CXCR3 pathway[1]
2. Inhibition of DPP4 increases CXCL9/10, leading to the recruitment of CXCR3 and NK/T cells

MECHANISM OF ACTION IN AML



Direct inhibition of DPP8/9 induces procaspase 1 pathway cleaving Gasdermin to induce pyroptosis in human myeloid cells[2]

PRECLINICAL DATA



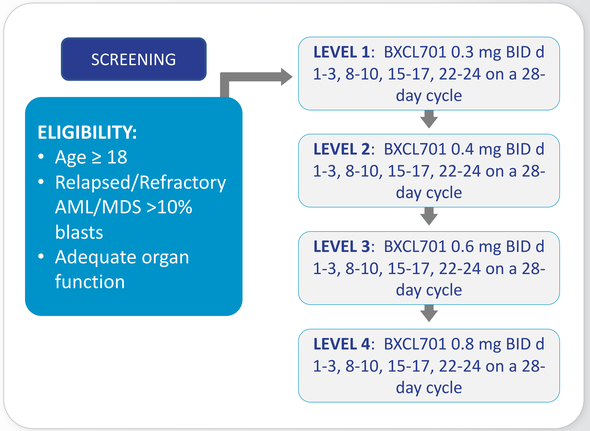
A. BXCL701 reduces tumor growth and increases survival of mice in an MV4-11 AML xenograft model

B. BXCL701 activity in combination in KG-1 xenograft model

C. DPP9 gene copy number correlates with BXCL701 cytotoxicity in human leukemic cell lines number

STUDY DESIGN

- Phase 1 trial that utilizes the oral agent BXCL701 in a standard 3+3 dose escalation format (schema follows)
- Dosing occurs days 1-3, 8-11, 15-17, 22-24 of each 28-day cycle
- Patients check blood pressure prior to each dose



KEY INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA

- Age ≥18
- Relapsed or Refractory AML OR r/r MDS with blast count 10-20% who have received at least 4 cycles of hypomethylating agent
- ECOG ≤2
  Creatinine Clearance ≥30 mL/min
- Total bilirubin ≤1.5x ULN
- ALT and AST ≤3x ULN
- EF >35%
- WBC <25,000 / µl; hydroxyurea permitted for first cycle

EXCLUSION CRITERIA

- Patients with Acute Promyelocytic Leukemia
- Active CNS disease (can be previously treated)
- Patients with prior treatment within 2 weeks or 5 half-lives prior to first dose of study medication
- Patients <100 days from allogeneic bone marrow transplant or active graft-versus-host disease
- Patients taking a gliptin for diabetes (sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin)
- Patients with a history of orthostatic hypotension with baseline SBP <100 or history of uncontrolled hypertension
- Concurrent active malignancy

OBJECTIVES

Primary Objectives

- To evaluate the safety of BXCL701 in AML or MDS with >10% blasts
- To determine the MTD or RP2D of BXCL as a single agent

Secondary Objectives

- To estimate Response Rates (CR, CRi, PR, MPFS, HI)
- To estimate Overall Survival and Duration of Response
- To assess pharmacokinetics at this dosing schedule

CORRELATIVE STUDIES

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1. Monitor circulating lymphocyte markers at multiple time points of BXCL administration evaluating T-cells (CD45, CD3, CD4, and CD8), regulatory T-cells (CD4+CD25+FOXP3+), NK-cells (CD56), and monocytic/myeloid cells (CD14, CD16, CD11b, HLA-DR)
2. Evaluate cytokine response at different time points during treatment. Cytokines evaluated will be G-CSF, GM-CSF, IFN-gamma, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-18, MIP-1 alpha, MIP-1 beta, MCP-1, TNF-alpha, TNF-beta, BDNF, Eotaxin-1, Factor VII, ICAM-1, IL-1 alpha, IL-1 beta, IL-1ra, IL-12p40, IL-12p70, IL-15, IL-17, IL-23, MMP-3, MMP-9, SCF, VEGF
3. Evaluate staining for DPP4, DPP8, DPP9 and FAP on all bone marrow samples throughout the study
4. Evaluate Copy number variants of DPP9 at multiple timepoints to determine its use as a biomarker

CONCLUSION

The trial is currently open and continuing to enroll

CONTACT INFORMATION

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REFERENCES

[1]Fitzgerald AA et al. J Immunother Can 2021, 9(11):e002837
[2]Agarwal et al. SITC 2022 Abstract #25