Robust In vivo Synergy Between the Anti-CD33 ADC IMGN779 and the FLT3 Inhibitor Quizartinib in Human FLT3-ITD AML Models

Kristy Watkins, Lee Flaherty, Rebecca McCarthy, Katherine Francisco, Sharlene Adams, Callum Sloss, Angela Romanelli
ImmuNoGen Inc., Waltham, MA, USA

Abstract PF190

INTRODUCTION

• Acute myeloid leukemia (AML) patients harboring a FLT3 Internal Tandem Duplication (FLT3-ITD) have a poor prognosis and high rates of relapse following treatment with standard agents.
• Midostaurin has been recently approved for the treatment of newly-diagnosed FLT3-ITD AML.
• Additional FLT3 inhibitors, such as the more potent and specific quizartinib, are additional FLT3 inhibitors, such as the more potent and specific quizartinib, are needed for patients with FLT3-ITD-positive leukemia (NCT02674763).

In vitro Studies:
FLT3-ITD AML cell lines (MV4-11 and Molm-13) were cultured in supplier recommended media. Cells do not show the upregulation of the anti-apoptotic protein Mcl-1.

In vivo Studies:
Two disseminated FLT3-ITD AML cell lines (MV4-11 and Molm-13) were engrafted into immunodeficient mice. Treatment began 7 days after AML cell engraftment in the Molm-13 model and 21 days in the MV4-11 model.

METHODS

• Treatment with IMGN779 increased Mcl-1 levels following treatments with IMGN779, 0.010 mg/kg, QWx3, Day 7 start and quizartinib led to fewer viable cells than either single agent treatment at 72 hours.

CONCLUSIONS

• The combination of IMGN779 and quizartinib results in a robust anti-leukemic effect in vivo.
• Mcl-1 is upregulated with IMGN779 treatment; the addition of quizartinib precludes this increase.
• The combination effect in vitro correlates with quizartinib-driven decreases in anti-apoptotic signaling, and decreases in the DNA repair effector Rad51.
• These findings support the testing of the combination of IMGN779 and quizartinib in both preclinical and clinical settings.

REFERENCES:
6. The combination of IMGN779 + Quizartinib Prolongs Survival in Molm-13 Disseminated Xenograft Model

The Treatment of IMGN779 + Quizartinib.

The Combination of IMGN779 + Quizartinib Prolongs Survival in Molm-13 Disseminated Xenograft Model

The Combination of IMGN779 + Quizartinib Prolongs Survival in MV4-11 Disseminated Xenograft Model

The Combination of IMGN779 + Quizartinib Prolongs Survival in MV4-11 Disseminated Xenograft Model

Quizartinib Decreases Tyrosine Kinase Signaling in a Dose-Dependent Manner

Treatment with quizartinib led to dose-dependent decreases in the following proteins:
- McI-1 (anti-apoptotic)
- p-Stat5 (pro-survival, pro-proliferative)
- p-Erk (pro-proliferative)
- Rad51 (DNA repair proteins)

In addition, quizartinib induced a dose-dependent decrease in apoptosis as shown by an increase in expression of the following proteins:
- Cleaved Caspase3 (induces apoptotic signaling)
- Cleaved PARP (induces apoptotic signaling)
- Rad51 (DNA repair protein)

Quizartinib Reverses IMGN779 Induced Increases in the Anti-Apoptotic Protein, MCL-1

Treatment with IMGN779 increased Mcl-1 levels.

The combination of quizartinib and IMGN779 decreased Mcl-1, p-Stat5, p-ERK1/2, and Rad 51 in a manner similar to that of quizartinib alone.

Crucially, in spite of treatment with IMGN779, the combination-treated cells do not show the upregulation of the anti-apoptotic protein Mcl-1.

Reduced levels of Mcl-1, decreases in a cell’s DNA damage response (Rad51) and pro-survival signaling (p-STAT5), may be responsible for the increased cell killing of IMGN779 when combined with quizartinib.