The Combination of IMGN632, a CD123-Targeting ADC, with Venetoclax Enhances Anti-Leukemic Activity

**In vitro and Prolongs Survival In pre- Clinical Models of Human AML**

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**INTRODUCTION**

- **IMGN632** is a CD123-targeting antibody drug conjugate composed of a humanized anti-CD123 mAb, which binds to leukemic cells, linked via a stable linker to a monomethyl auristatin E payload. IMGN632 USA phase I/II trial (NCT03386513) in patients with relapsed/refractory AML (acute myeloid leukemia) or MDS/AML phenotypic myelodysplastic disease cell replacement, demonstrating responses across a wide range of doses.
- Venetoclax, a BCL-2 inhibitor which lowers the apoptotic threshold in AML cells, was recently approved for elderly AML patients in combination with azacitidine.
- Combining these potentially synergistic anti-leukemic mechanisms in pre-clinical AML models, we hypothesized that the BCL-2 inhibition would synergize with the pro-apoptotic effects of IMGN632 induced by MDAK.

**Methods**

- In vivo Studies: EOL-1 and MV4-11 AML xenograft, Molm-13 and KG-1 AML cell line-derived subcutaneous AML xenograft models, with either vehicle vehicle (IMGN632, IC50; venetoclax, EOL-1 IC50: MV4-11 IC50: KG-1 IC50: or IMGN632 plus venetoclax for 40, 72 and 96 h). The percentage of viable and dead cells by fluorophore-conjugated, anti-leukemic Caspase 3 mononuclear antibody were quantified by flow cytometry.
- In vitro Studies: IMGN632 and venetoclax cytotoxicity was evaluated by Trypan blue exclusion. Drug combination tests were run for each cell line. The median CI (CI50) was calculated in CalcuSyn by comparing the expected additive fractional affected value for a combination dose pairing to its observed fractional affected value. CI50 is between 1 and 0.4 representing "additive" combination effects, while 0.4 is between 0.3 and 0.0 representing "synergistic" combination effects.

**Results**

- In vivo Studies: IMGN632 and venetoclax treatment prolonged survival in four AML xenograft models, prolonging survival in all four AML cell lines assessed.
- The combination of IMGN632 and venetoclax has been shown to be safe and well tolerated in clinical trials.

**Conclusions**

- In vivo, the combination of IMGN632 and venetoclax increases the percentage of both apoptotic and dead AML cells in vitro.
- Median CI values across a dynamic range of IMGN632 and venetoclax in vitro treatments indicate additive-to-synergistic combinatorial cytotoxic effects in all four AML cell lines assessed.
- In vivo, the combination of IMGN632 and venetoclax prolongs survival and enhances anti-leukemic activity in subcutaneous and disseminated AML CDX models and in AML PDX models.
- These findings support testing the combination of IMGN632 and venetoclax (ECL-2 inhibitors) in a clinical trial in AML patients.