The Anti-Myeloma Activity of TTI-621 (SIRPaFc), a CD47-Blocking Immunotherapeutic, is Enhanced When Combined With a Proteasome Inhibitor

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TTI-621 (SIRPaFc): A Novel Biologic that Blocks the CD47 “Do Not Eat” Signal

- CD47 binds to SIRPα on the surface of macrophages and delivers a “do not eat” signal to suppress phagocytosis.
- Tumor cells frequently overexpress CD47 and exploit this pathway to evade macrophage-mediated destruction.
- Blocking CD47 using a soluble decoy receptor (SIRPaFc) has emerged as a promising strategy to neutralize the suppressive effects of CD47 and promote the eradication of tumor cells.
- TTI-621 (SIRPaFc) exhibits potent in vivo anti-tumor activity in mouse models of AML, lymphoma and multiple myeloma.
- In this study, we have elucidated the effect of combining CD47 blockade using TTI-621 with FDA-approved proteasome inhibitors.
- TTI-621 is currently in Phase I clinical trials for hematological malignancies, including multiple myeloma (NCT02663518) and solid tumors (NCT02890368).

Bortezomib, Carfilzomib and Ixazomib Enhance TTI-621-Mediated Phagocytosis of Multiple Myeloma Cells In Vitro

Phagocytosis of multiple myeloma cells was assessed using flow cytometry. Data are presented as fold over isotype to account for increased autofluorescence of bortezomib-treated cells. Abbreviation: Fc, Fc Domain.

Proteasome Inhibition Leads to Upregulation of Putative “Eat” Signals on the Tumor Cell Surface

Studies are currently ongoing to evaluate the functional relevance of these markers.

TTI-621 Efficacy In Multiple Myeloma Xenografts is Enhanced in Combination With Proteasome Inhibitors

- Proteasome Inhibition Enhances Phagocytosis of a Multiple Myeloma Cell Line that is Minimally Responsive to TTI-621.
- Bortezomib Enhances Phagocytosis by SIRPaFc With an IgG1 or IgG4 Fc Domain.

Conclusions

- Proteasome inhibitors enhance the phagocytosis of multiple myeloma cells by SIRPaFc with either an IgG1 (TTI-621) or IgG4 (TTI-621) Fc domain.
- Preliminary data suggest that tumor cells treated with proteasome inhibitors upregulate putative “eat” signals.
- TTI-621 anti-myeloma activity in vivo is further enhanced by combination with a proteasome inhibitor.
- TTI-621 monotherapy is currently being evaluated in a Phase Ib study in patients with hematological malignancies, including multiple myeloma. These data provide a rationale to evaluate a combination study of TTI-621 and a proteasome inhibitor in multiple myeloma patients.