Title

A first-in-class CD64-targeting ADC for the selective depletion of pathogenic monocytic cells in hematologic and solid tumors

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Abstract

Background

Cells of the monocytic lineage contribute to disease progression and treatment resistance in multiple malignancies, including chronic myelomonocytic leukemia, monocytic acute myeloid leukemia, and solid tumors enriched in tumor-associated macrophages. Leukemic monocytes and tumor-associated macrophages often exhibit a highly differentiated, low-proliferative phenotype that is refractory to standard chemotherapies and limits the efficacy of immune checkpoint blockade in indications such as triple-negative breast cancer, pancreatic ductal adenocarcinoma, and glioblastoma. Identifying druggable targets shared across the monocytic differentiation spectrum, together with payloads capable of efficiently killing these cells, is therefore a promising strategy to overcome monocyte-driven resistance with Antibody-Drug Conjugates (ADCs).

Methods

An ex vivo patient-derived micro-avatar platform was used to screen surface targets and cytotoxic payloads in leukemic monocytes and tumor-associated macrophages from hematologic malignancies and solid tumors. Expression and internalization of candidate targets were quantified in primary monocytic cells, and a panel of antibody–drug conjugates incorporating distinct payload classes were evaluated across monocytic cell lines, primary leukemic monocytes, and tumor-associated macrophages ex vivo, as well as in multiple in vivo models of leukemia and solid tumors, including humanized mouse models with

established xenografts. Safety and tolerability were assessed using both the human-specific and a murine-specific surrogate antibody-drug conjugate targeting CD64 in mice.

Results

Target/payload screening identified CD64 as a highly expressed, efficiently internalizing receptor on patient-derived monocytic cells, and PNU-159682 as the payload with the most favorable mechanism of action for depleting monocytic populations. In contrast, antibody-drug conjugates incorporating clinically validated payloads such as Exatecan or MMAE showed minimal or no activity against malignant monocytes and tumor-associated macrophages, revealing a non-obvious vulnerability of these cells to PNU. The CD64-targeting PNU-based ADC demonstrated picomolar potency in monocytic cell lines in vitro and robust cytotoxicity against primary leukemic monocytes and tumor-associated macrophages ex vivo, with marked tumor growth control and selective depletion of tumor-associated macrophages in multiple leukemia and solid tumor models in vivo, including efficient clearance of tumor-associated macrophages from the tumor microenvironment after a single dose in a humanized xenograft model. Across efficacy-relevant dose ranges, both the human-specific and murine surrogate constructs showed no evidence of significant on-target or off-target toxicity and exhibited favorable tolerability profiles in preclinical safety studies.

Conclusions

These data nominate CD64 as a tractable, lineage-restricted target and PNU-159682 as an optimal payload combination for selective depletion of pathogenic monocytic cells in cancer. The resulting CD64-directed PNU-based ADC demonstrates potent antitumor activity, efficient tumor-associated macrophage and leukemic monocyte depletion, and a favorable preclinical therapeutic index, supporting its further development as a strategy to overcome monocyte-mediated resistance in hematologic malignancies and solid tumors.