Background Studies have shown that ELANE- a neutrophil-derived serine protease – kills a wide range of cancer cells without harming non-cancer cells by cleaving CD95 to liberate the death domain. This liberated death domain interacts with histone H1, whose differential expression between cancer and non-cancer cell contributes to selective cancer killing. Here we leveraged this ELANE-mediated pathway to develop an optimized N17350 biologic, tested its effects on tumor development as a monotherapy and in combination with checkpoint inhibitors, and evaluated histone H1 as a potential biomarker for N17350 efficacy. Our findings underscore the viability of N17350 as a new therapeutic modality.

Methods For in vitro studies, human and murine cancer and non-cancer cells (cell lines, primary cells from healthy donors and ovarian cancer patients) were treated with N17350, and cell viability was quantified by calcein-AM and immunogenic cell death (ICD) markers. To evaluate histone H1 as a potential biomarker, we studied the correlation between H1 levels in cancer cells and N17350 killing and compared H1 levels in normal and tumor tissue microarrays. For in vivo studies, a single dose of N17350 was delivered intratumorally into CT26 (colon) and 4T1 (metastatic breast) and A549 (lung) tumors. Effects on primary (4T1, CT26, A549) and metastatic (4T1) tumor growth, immunology, and survival were assessed as a monotherapy or in combination with a checkpoint inhibitor (anti-CTLA4). CT26 tumor-free mice were rechallenged to examine immune memory.

Results N17350 selectively killed and induced ICD markers in all human and murine cancer cell lines tested and avoided resistance following repeated challenge. Histone H1 isoforms were upregulated with disease progression, and their increased levels in human cancer cells were correlated with enhanced killing by N17350 in vitro. A single intratumoral dose of N17350 eliminated a range of tumor sizes (100–500mm³), induced favorable innate and adaptive immunity, and conferred resistance to rechallenge in the immunologically hot CT26 model. N17350 regressed tumor growth, induced a CD8⁺ T cell-mediated abscopal effect to attack distal metastases, and enabled checkpoint inhibitor efficacy in the immunologically cold 4T1 model. N17350 also regressed tumor growth in a human A549 xenograft model.

Conclusions Taken together, our data demonstrate that N17350 selectively kills cancer cells, produces complete responses in mice, induces favorable innate/adaptive immunology, and identify histone H1 as a putative biomarker for efficacy. Thus, further studies in a clinical setting are warranted.

REFERENCE


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