Preclinical characterization of NKp30xBCMA, a novel class of NK-Cell Engagers

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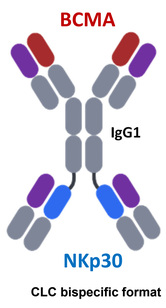
Background

Multiple myeloma (MM) is characterized by clonal expansion of malignant plasma cells. Although several new drugs for the treatment of MM have greatly improved survival, many patients are known to relapse and become refractory to all presently available therapies. B-cell maturation antigen (BCMA) is an excellent target in MM because its restricted expression in normal and malignant plasma cells from untreated and relapsed myeloma patients, but absent in all other main bone marrow cell subsets. We have discovered a first-in-class NK cell engager, CTX-4419, which binds to BCMA on MM cells and to the activating receptors NKp30 and CD16A (FcγRIIIA) on NK cells, and acts via redirecting NK cell killing towards tumor cells expressing BCMA. In contrast to other NK cell engagers, CTX-4419 and its affinity matured version, CTX-4419AM, do not require CD16A engagement to kill tumor cells. Additionally, CTX-4419 induces NK cell proliferation and lysis of tumor cells expressing high and low amount of antigen. Furthermore CTX-4419AM retains activity in the presence of high levels of BCMA ligands. Our NKp30xBCMA shows strong activity in an autologous setting when tested in bone marrow samples of MM patients and shows efficacy in a non-human primate model of plasma-cell depletion. Overall these data show that Compass novel class of NK cell engagers are strongly differentiated from conventional therapeutic antibodies and are promising candidates for MM treatment.

Results

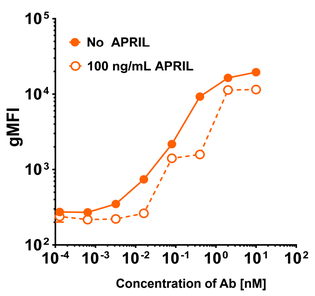
CTX-4419AM Directly Inhibits the Growth of MM Tumor Cells

CTX-4419AM



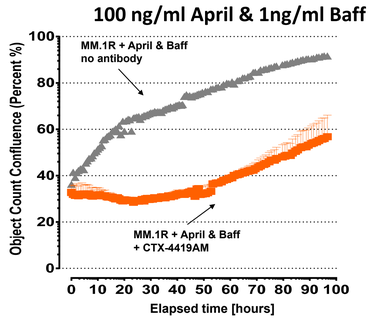
CLC bispecific format

The presence of April does not affect binding of CTX-4419AM to H929



Binding of CTX-4419AM was measured by flow cytometry in the presence or absence of soluble April.

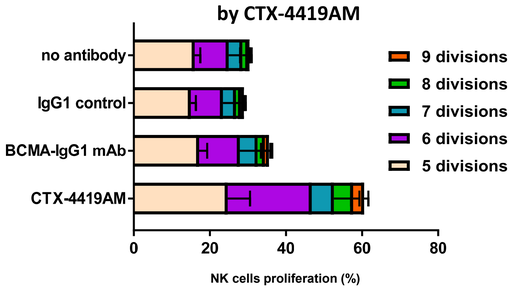
CTX-4419AM (10 pM) blocks tumor cell proliferation in the presence of 100 ng/ml April & 1ng/ml Baff



Tumor cell proliferation was monitored over 100 hours time by fluorescence imaging using an IncucCyte Live Cell analysis system.

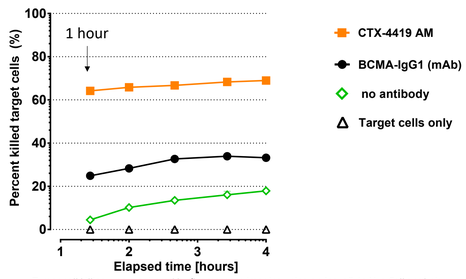
CTX-4419AM Induces Proliferation of NK Cells and Potent Tumor Cell Killing

NK cell proliferation induced by CTX-4419AM



NK cell proliferation after incubation of BCMA+ H929 myeloma cells compared as observed by CTV dilution at day 5.

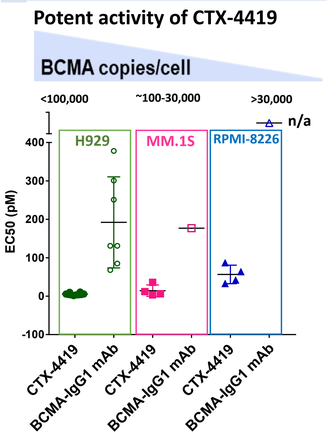
Targets: MM.1R in the presence of 100 ng/ml April & 1ng/ml Baff



Tumor cell killing was monitored by fluorescence imaging using an IncucCyte Live Cell analysis system. Percent killing was calculated by normalizing to the number of target cells only control group

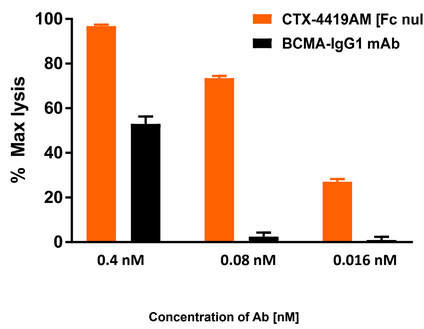
CTX-4419AM Induces Potent NK Cell Killing of BCMApos Tumor Cells with a Wide Range of Antigen Expression

Potent activity of CTX-4419



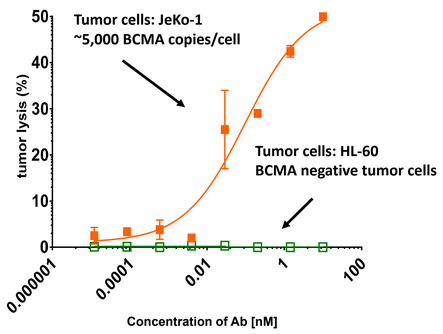
EC50 values of target cell lysis induced by CTX-4419AM using primary NK cells

Activity in the absence of CD16A engagement



Dose-response in percentage of max lysis of H929 lysis induced by CTX-4419AM [Fc null] or BCMA-IgG1 mAb using primary NK cells

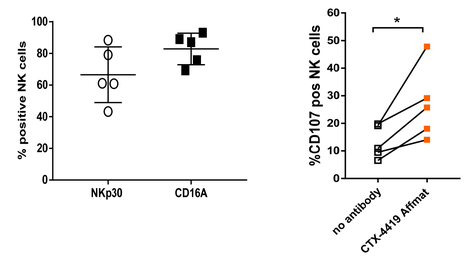
Activity towards BCMA^{low} tumor cells but not BCMA negative tumor cells



Primary NK cells were tested in a 4 hours killing assays against Jeko-1 or HL-60

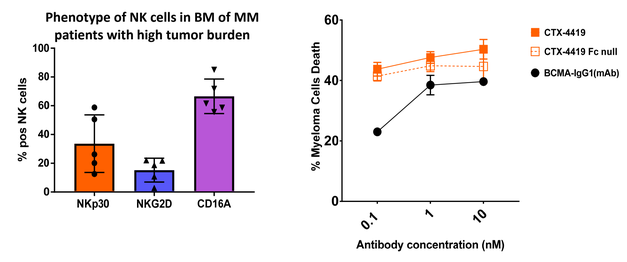
CTX-4419 Induces Potent Killing of Autologous Myeloma Cells from MM Patients

CTX-4419 enhanced function of peripheral NK cells from five MM patients



Expression of NKp30 and CD16a was assessed by flow cytometry on NK cells from MM patients (n=5). NK cells from MM patients (n=5) were tested against MM.1S tumor cells and CD107 degranulation was measured by flow cytometry.

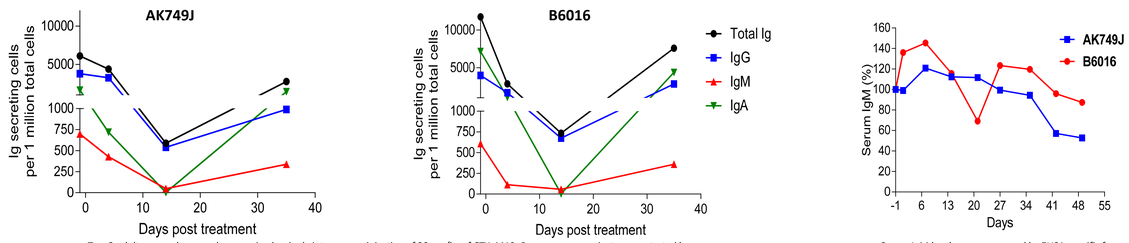
CTX-4419 induced killing of autologous MM cells by bone marrow NK cells



Expression of NKp30 , CD16 A and NKG2D was assessed by flow cytometry on NK cells from bone marrow of MM patients (n=5) with high tumor burden

Bone marrow aspirates were incubated for 4 hours with antibodies and death of MM tumor cells was measured by flow cytometry as decreased of CD138pos MM cells. Data was normalized to control wells without antibody

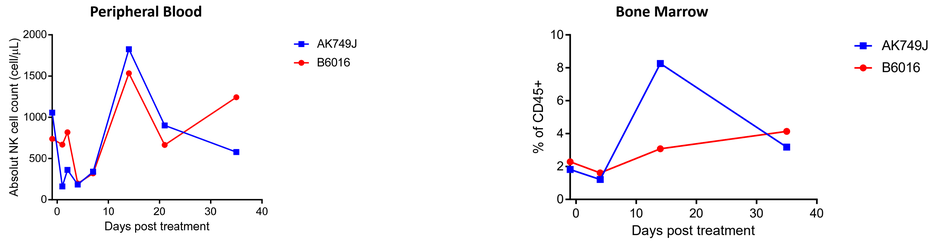
Single Dose of CTX-4419 Potently Depletes Immunoglobulin-Secreting Cells in Bone Marrow of Cynomolgus Monkeys and Decreases Serum IgM levels



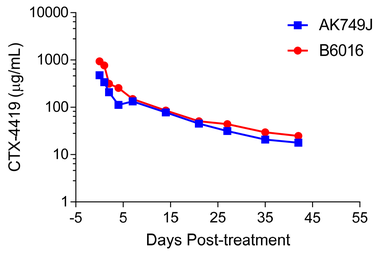
Two 2 adult cynomolgus monkeys received a single intravenous injection of 30 mg/kg of CTX-4419. Bone marrow aspirates were tested by ELISPOT to determine the number of immunoglobulin-secreting cells.

Serum IgM levels were measured by ELISA specific for monkey IgM detection

CTX-4419 Induces NK Cell Expansion in the Peripheral Blood and Bone Marrow of Cynomolgus Monkeys



CTX-4419 Displays IgG-like Pharmacokinetics in Cynomolgus Monkeys



- β-phase half-life ~ 16 days

Levels of CTX-4419 over the course of the experiment were measured using BCMA-specific ELISA.

Conclusions

- CTX-4419, a first-in-class NKp30xBCMA bispecific, induces cytokine production, NK cell proliferation and potent tumor cell killing of target cells with high, medium, & low BCMA
- CTX-4419 differentiates from BCMA-IgG1 mAbs for its capability to activate NK cells in the absence of CD16A engagement
- CTX-4419 induces potent depletion of plasma cells in cynomolgus monkeys
- Compass highly modular platform has the potential to tailor TAA and NK cell receptors to target multiple indications