Background| Autologous CAR-T therapy has revolutionized the treatment of multiple myeloma (MM), but many patients still face obstacles in accessing these therapies due to manufacturing limitations and the absence of allogeneic alternatives. A major obstacle faced by allogeneic cell therapies is allograft rejection. While elimination of class I HLA expression via deletion of the beta-2 microglobulin gene (b2m) abrogates graft-versus-host disease (GvHD), it renders the off-the-shelf CAR-T highly susceptible to the host NK cell killing due to the absence of ‘self’ signals.

Methods| To overcome this limitation, we investigated the use of an anti-CD38 IgG1 monoclonal antibody (CD38 mAb) to deplete NK cells. CD38 is highly expressed on NK cells as well as plasma cells. Clinical data suggests that treatment with CD38 mAb induces antibody dependent cellular cytotoxicity (ADCC), leading to significant depletion of NK cells in patients with MM who are in refractory or relapsed stages. Based on these findings, we hypothesized that CD38 mAb could protect allogeneic T cells from NK-mediated cytotoxicity.

Results| Here, we show that in vitro treatment with CD38 mAb effectively depletes 70% of NK cells from peripheral blood mononuclear cells (PBMC) obtained from healthy donors. Importantly, this treatment does not have a significant impact on other hematopoietic cells such as T, B cells and monocytes. Furthermore, we observed a 50% reduction in NK-mediated cytotoxicity against CD38 and b2m double knock-out (DKO) allogeneic T cells when treated with CD38 mAb, compared to the untreated control.

Similarly, PBMC isolated from patients with MM and treated with the CD38 mAb regimen displayed a significant decrease in the NK cell population, resulting in impaired cytotoxicity against DKO allogeneic T cells. To further validate our findings, we utilized a mouse model in which human NK cells were engrafted and retained their ability to reject DKO T cells upon injection. In vivo administration of CD38 mAb in these mice showed a dose-dependent depletion of engrafted NK cells in the blood and peripheral tissues, leading to a median reduction of 60% in NK-mediated killing of DKO allogeneic T cells.

Conclusions| Collectively, our in vitro and in vivo data strongly support the notion that pharmacological depletion of NK cells through CD38 mAb treatment represents a promising approach to avoid allorejection of CAR-T products. These findings provide valuable insights into the potential use of CD38 mAb as a strategy to enhance the safety and efficacy of allogeneic CAR-T cell therapies.

Ethics Approval| The mouse study described in this abstract was approved by AstraZeneca’s Ethics Board and met with regards to the humane treatment of animals.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0432