Characteristics & Positioning of Autologous NK Cell Therapies in Relation to Allogeneic Ditto

BACKGROUND

XNK Therapeutics (XNK) focuses on the development of *autologous* NK cell-based therapies. The reasons for XNK's ambition to stay strong in the autologous space are several and are summarized in this document. With both allogeneic and autologous NK cell products approaching the market, XNK's position is that these do not necessarily constitute competing strategies, but should rather be seen as complementary, each with their own unique characteristics and suited for mostly non-overlapping patient populations.

As outlined by Nahi et al (*ref*), the rationale for using allogeneic NK cells was initially a consequence of insights into the molecular specificity of NK cells, in particular their capacity to mediate missing self-reactivity. Applicability was further supported by findings on the role of NK cells in haploidentical hematopoietic stem cell transplantation (HSCT). More recently, the 'off-the-shelf' potential has in a significant way contributed to the fact that allogeneic NK cell immunotherapy strategies currently dominate the field. Although fewer studies currently encompass the use of autologous NK cells, the concept is not new. Adoptive transfer of autologous NK cells to cancer patients was studied already in the mid-1980s. One reason for the mixed results being the unfavourable clinical setting in which they were originally used *e.g.* in treatment of patients with refractory solid tumors, such as progressive stage IV melanoma or renal cancer.

Adding potential strengths to the use of autologous NK cells in clinical settings, XNK has developed a unique manufacturing process which allows efficient expansion and activation of NK cells directly derived from cancer patients. This process has demonstrated feasibility both in the context of hematological malignancies and solid tumors. With the technological breakthrough of a robust production method, the advantages of an autologous approach may be explored in patient populations favoured by such advantages. Below, XNK outlines how autologous NK cell-based therapy complement, and differentiate, from treatment with allogeneic NK cells and how its unique features can support a positioning within the consolidation, maintenance and MRD segments.

DIFFERENTIATION OF AUTOLOGOUS NK CELL-BASED THERAPY IN RELATION TO ALLOGENEIC APPROACHES

We see several benefits which justify further development and commercialization of autologous NK cell-based products in a number of cancer patient populations/indications. Benefits include, but are not limited to, the following:

- The well-established safety, which in addition to providing obvious benefits to patients also means regulatory advantages and de-risking
- The possibility and ease of repeat dosing
- The possibility of treating patient populations in which immuno-suppressive pre-treatment is not advisable or possible
- Potential for longer effect duration due to limited risk for elimination of cells by the patient's immune system

These four areas currently differentiate autologous NK cell treatment in relation to allogeneic NK cell products.

A product based on the patient's own cells are inheritably more likely accepted and safer than a product based on donor cells. Regulators are wary of safety risks and autologous cell therapies therefore comes with a regulatory advantage.

In situations where the cancer patient is first treated with an established therapy with considerable efficacy but where recurrence rates are high, the autologous NK cell-based therapy may provide an attractive way to consolidate such treatment and fight MRD. As an example, such initial debulking may come from induction therapy and autologous HSCT (as seen in our lead indication where evencaleucel is currently evaluated as consolidation treatment in combination with a CD38 mAb in newly diagnosed multiple myeloma patients following autologous HSCT). The safety profile and potential for repeat dosing open-up the opportunity for longer term maintenance treatment to reduce recurrence and relapse.

In populations where the initial de-bulking treatment is not scheduled immediately upon diagnosis or takes some time to perform or take effect, there will be sufficient time to manufacture an autologous consolidation therapy product.

Allogeneic products have the potential to offer quick, deep and dramatic effects. One worry, however, relates to persistence. While XNK's autologous product candidate evencaleucel has been seen to remain in the body for at least 4 weeks, allogeneic cells are expected to be cleared more rapidly. Should gene modification approaches successfully increase persistence of donor-derived allogeneic cells, safety might become more challenging.

Before administering an allogeneic cell product, patients will typically be given an immunosuppressive pre-treatment. In certain patient populations this is not advisable. This would include *e.g.* patients with ongoing infections, impaired organ function and those of poor general condition. These populations would still

be addressable by an autologous NK cell treatment where such immunosuppressive pre-treatment is not necessary.

With robust vein-to-vein and manufacturing processes, it is anticipated that production and distribution costs will not differ dramatically between autologous and allogeneic products.

XNK has decided to focus its strategies on expected synergistic effects of its NK cell therapy product with different types of cell engagers providing enhanced target cell specificity. Several ADCC competent monoclonal antibodies are already successfully put on the market and, as a result, well characterized and documented. XNK's autologous NK cells have the potential of boosting the effect of the ADCC competent mAbs and to mitigate the risk of NK cell depletion. Combining with bi- and tri-specific engagers in development might equally be of interest.

SUMMARY

XNK sees that allogeneic and autologous NK cell products can contribute in different ways and in different populations to future treatment of cancer. The strategies will typically not compete but rather complement each other. Based on the above rationale and the fiercely competitive allogeneic space, XNK is currently firmly positioned in and committed to the development of autologous NK cell-based therapies.