SUMMARY ~~OF THE INVENTION~~

[05a] In a first aspect of the present disclosure, there is provided a use of an agonistic anti-CD137 antibody for the preparation of a medicament for enhancing the anti-tumor effect of an antibody directed against a tumor antigen that induces or up-regulates expression of CD137 on NK cells, wherein said medicament is to be administered a period of time after said antibody directed against a tumor antigen that induces or up-regulates expression of CD137 on NK cells in a cancer patient is administered.

[06] Methods are provided to enhance the anti-tumor effect of monoclonal antibodies directed against tumor antigen(s). In the methods of the ~~invention~~present disclosure, ADCC function is specifically augmented, which in turn enhances target cell killing, by sequential administration of an antibody directed against one or more tumor antigens, and an agonistic antibody against one or several inducible costimulatory molecules on NK cells.

[07] An individual diagnosed with a tumor is first administered a tumor-directed antibody. After a period of time NK cells which are innate immune effector cells critical for ADCC upregulate expression of inducible costimulatory molecules such as CD137, OX40, GITR, CD30 or ICOS. Subsequently, a second antibody is administered targeting the induced costimulatory molecule on NK cells (including but not limited to anti-CD137, anti-OX40, anti-GITR, anti-CD30 or anti-ICOS). In some embodiments, expression of the aforementioned costimulatory molecules is evaluated following administration of the tumor-directed antibody, in order to determine the optimal time for dosing the second agent. Alternatively a timing period is determined empirically, and generally applied. The combination of agents and their sequential administration is shown to provide for a level of tumor-specific, therapeutic synergy that is not observed with administration of the single agents alone. The method specifically enhances the anti-tumor function of monoclonal antibodies directed against tumor antigens. Because the second antibody targets costimulatory molecules that have been inducibly expressed on NK cells by the tumor-directed antibody, this methods allows specific stimulation of NK cells which are implicated in ADCC-mediated killing of the tumor cells, while sparing other NK cells, thereby limiting potential non specific side effects.

[08] In some embodiments of the present disclosure~~invention~~, the inducible costimulatory molecule is CD137. In such methods, an individual diagnosed with a tumor is first administered a tumor-selective antibody. After a period of time sufficient to upregulate expression of CD137 in immune system cells, a second agent is administered, which agent is an agonist of CD137. In some embodiments the level of CD137 expression on blood cells is determined prior to each administering step, where an increase in expression is indicative that the second agent may be administered.

BRIEF DESCRIPTION OF THE DRAWINGS

[09] Figures 1A-1C. Rituximab induces CD137 upregulation on human NK cells following incubation with CD20-positive tumor B cells. Peripheral blood from three healthy donors was analyzed for CD137 expression on $CD3^{-}CD56^{+}$ NK cells after 24 hour culture with lymphoma cell lines and trastuzumab or rituximab. (A) shows the percentage of $CD137^{+}$ cells among $CD3^{-}CD56^{+}$ NK cells from three healthy donors cultured with $CD20^{-}$

13. The use according to claim 12, wherein the cancer is or comprises an acute lymphoblastic leukemia (ALL), a chronic lymphocytic leukemia (CLL), a colorectal cancer, a hairy cell leukemia, a marginal zone lymphoma (MZL), a myelogenous leukemia, a non-Hodgkin's lymphoma or a squamous cell carcinoma.

~~14. A kit for use in enhancing the anti-tumor effect of an antibody directed against a tumor antigen that induces or up-regulates expression of CD137 on NK cells comprising i) said antibody directed against a tumor antigen that induces or up-regulates expression of CD137 on NK cells and ii) an agonistic anti-CD137 antibody, each of which is in the form of lyophilized formulations or aqueous solutions in an article of manufacture.~~

~~15. The kit of claim 14 wherein each of the two active agents is formulated in a compatible pharmaceutical carrier, in an appropriate container that is labeled for the treatment of a cancer, in a pack or dispenser device containing one or more unit dosage forms containing the two active agents.~~

~~16. The kit of claim 14, comprising a unit suitable for measuring expression of CD137on NK cells.~~

~~17. The kit of claim 14, further comprising buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.~~

~~18. A kit for use in treating cancer comprising a pack or dispenser device containing one or more unit dosage forms of i) an antibody that is directed against a tumor antigen that induces or up-regulates expression of CD137 on NK cells; and ii) an agonistic anti-CD137 antibody, each of which is in the form of lyophilized formulations or aqueous solutions in an article of manufacture.~~

~~19. The kit of claim 18, comprising a unit suitable for measuring expression of CD137on NK cells.~~

~~20. The kit of claim 18, further comprising buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.~~

~~21. Use of i) an antibody that is directed against a tumor antigen that induces or up-regulates expression of CD137 on NK cells; and ii) an agonistic anti-CD137 antibody, for the manufacture of a kit for the treatment of cancer, each of which is in the form of lyophilized formulations or aqueous solutions in an article of manufacture.~~

~~22. The use of claim 21 wherein each of the two active agents is formulated in a compatible pharmaceutical carrier, in an appropriate container that is labeled for the treatment of a cancer, in a pack or dispenser device containing one or more unit dosage forms containing the two active agents.~~

~~23. The use of claim 21, comprising a unit suitable for measuring expression of CD137on NK cells.~~

~~24. The use of claim 21, further comprising buffers, diluents, filters, needles, syringes, and package inserts with instructions for use.~~