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SNT-20109 INDUCES PROTECTIVE IMMUNITY IN THE MURINE SYNGENEIC TUMOR CELL LINE, CT26: A DUAL APPROACH OF DIRECT CYTOTOXICITY AND DEFINED IMMUNE ACTIVATION

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Background Despite considerable advances in cancer immunotherapy, it has proven difficult to effectively target ‘cold’ tumors with limited immune infiltration. Chimeric antigen receptor T cells (CAR-T cells) are one potential solution; however, their clinical use has been confined to treating hematologic malignancies partly due to their physical exclusion in the context of solid tumors. Cytokine-based therapy has shown significant potential in pre-clinical models, yet its clinical utility has been marked by limited efficacy and significant toxicities. This approach also fails to act directly on the tumor, instead relying on in situ immune responses to drive cytotoxicity and control tumor growth. In contrast, chemotherapy offers direct and robust cytotoxicity, but often at the cost of suppressing the immune response, which inhibits the development of long-lasting anti-tumor immunity. Thus, there is still an urgent need to find an optimal balance between direct tumor control and the generation of a robust immune response to combat cancer more effectively.

Methods SNT-20109 was assessed using an engineered CT26 tumor model that expresses our payload under a doxycycline promoter. We initiated tumor models by subcutaneously injecting engineered or control CT26 cells into the right flanks of 6–8 weeks old BALB/c mice. After the tumors reached ~100 mm³, the mice were randomized into treatment groups and doxycycline-containing chow was administered for a period of 7 days.

Results Following doxycycline activation, SNT-20109 demonstrates durable in vivo efficacy, consistently demonstrating significant tumor growth inhibition (TGI) and the majority of mice (9/10) showing complete regression. Importantly, mice treated with SNT-20109 exhibit a considerable survival advantage over control mice.

SNT-20109 drives a unique immunological cascade, typified by the hallmarks of immunogenic cell death (ICD) including cytotoxicity, enhanced membrane permeability and release of DAMPs. Moreover, in addition to ICD, SNT-20109 drives the robust production of pro-inflammatory cytokines and chemokines with known antitumoral effects not typically seen following ICD. The unique interplay of ICD and cytokine/chemokine release induced by SNT-20109, activates and attracts antigen-specific T cells to the tumor microenvironment, which is evident by an increase in activated, antigen specific T cells and significant TGI in the distal untreated tumors when co-administered with aPD-1, demonstrating a pronounced abscopal effect.

Conclusions SNT-20109 induces an innovative form of enhanced-ICD that has never before been characterized. The therapeutic potential of this approach presents an exciting avenue for future cancer treatment investigations.

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