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Novel monoclonal antibody therapeutics for metastatic castration resistant prostate cancer.

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[New Targets and New Technologies \(IO\)](#)

Category:

Developmental Immunotherapy and Tumor Immunobiology

Meeting:

[2019 ASCO Annual Meeting](#)

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Author(s): Maloy Ghosh, Kavitha Iyer Rodrigues, Sunit Maity, Sanghamitra Bhattacharjee, Yogendra Manjunath, Subhra Prakash Chakrabarty, Ashvini Kumar Dubey, Anurag Tiwari, Sathyabalan Murugesan, Vivek Halan; Zumutor Biologics, Bangalore, India; Zumutor Inc, Woburn, MA

Abstract Disclosures

Abstract:

Background: Therapeutic potential of innate immunity comprising Natural killer cell based targets are beginning to unravel the complexity of immune responses. NK cells recognize and induce cytotoxicity of wide range of target cells, such as, tumor cells without prior antigen sensitization. In this study, we have studied Lectin-like transcript 1 (LLT1), a member of the C-type lectin super family, is expressed on target cells and various immune cells. LLT1 isoform 1, is known to interact with CD161, a critical receptor on NK cells. CD161 is expressed on most of human NK cells, NK-T cells, $\gamma\delta$ T cells and so on. Tumors exploit the CD161-LLT1 interaction to evade host defense mechanism ("DO NOT KILL" signal); indicating LLT1 as an attractive immunotherapeutic strategy.

Methods: Prostate cancer cell lines and other tumor cell lines were used to evaluate novel anti LLT1 antibodies for therapeutic potential - IFN γ production assays and tumor cell death assays were carried out. *In vivo* efficacy of these antibodies were established using PC3 xenograft in humanized mouse model (HuNOG-EXL). **Results:** Human androgen independent prostate cancer cell line, PC3 was studied for LLT1 expression and interactions with immune cells, to understand role of LLT1 in metastatic castration resistant prostate cancer (mCRPC). Overexpression of LLT1 on tumor cells was influenced by cytokines and various TLRs. Inhibition of CD161-LLT1 interaction with novel anti LLT1 antibodies leads to IFN γ production and consequent NK cell mediated cytotoxicity – hall mark of anti-tumor responses. Disruption of LLT1 - CD161 innate immunity axis with anti LLT1 antibody releases the break on NK cell cytotoxicity and hence,

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established a new therapeutic option. PC3 xenograft on HuNOG mouse revealed *in vivo* efficacy of LLT1 antibody. Significant tumor growth reduction was observed with specific anti LLT1 antibodies alone and in combination with check point antibodies. Thus, synergistic tumor growth reduction was established by combinatorial application of anti LLT1 antibody and PD1/PDL1 axis inhibitors. **Conclusions:** PC3 xenograft study and other results point to therapeutic opportunities in metastatic castration resistant prostate cancer, a disease condition which needs improved patient outcomes. The ligation of CD161/LLT1 will serve as a new immuno-oncology pair regulating innate and adaptive immune responses; novel human antibodies against LLT1 described here will bring therapeutic benefit to patients in need.

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