Leronlimab, a humanized monoclonal antibody to CCR5, blocks breast cancer metastasis and enhances cell death induced by DNA damaging chemotherapy

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Abstract

Purpose of the study. To assess binding and functional interaction of the humanized monoclonal antibody to CCR5 (Leronlimab) with human breast cancer cell lines. The G protein coupled receptor CCR5, is normally expressed on a subset of T cells and serves as a co-receptor for HIV infection. During malignant transformation CCR5 expression is known to increase in a number of cancers (breast cancer (BCa), prostate cancer, colon cancer, melanoma). CCR5 targeted cancer clinical trials using small molecular inhibitors opened to accrual in late 2018. CCR5 is expressed in >50% of human BCa, primarily in triple negative BCa. Its expression in human BCa correlates with poor outcome and CCR5+ BCa epithelial cells have characteristics of cancer stem cells, forming mammospheres and initiating tumors with >60-fold greater efficiency in mice. Reintroduction of CCR5 expression into CCR5 negative BCa cells promotes tumor metastasis and induces DNA repair gene expression and activity. The CCR5 inhibitor Leronlimab has been used for treatment of >600 patients with HI, including meeting its primary endpoints in a phase III study, without significant adverse events reported. Results. Leronlimab bound to CCR5 expressed in human breast cancer cell lines with 98% efficiency. Leronlimab abrogated CCL5 induced CCR5+ flux and blocked CCL5 mediated invasion of MDA-MB-231 cells. Leronlimab blocks human breast cancer xenograft metastasis in mice. Leronlimab also augmented cell killing by DNA damage inducing agents including Doxorubicin. Conclusions. Leronlimab binds CCR5 in BCa cells, blocking breast cancer cellular invasion and tumor metastasis, and augmenting cell killing by DNA damage inducing chemotherapies. As CCR5 augments DNA repair and is expressed selectively on cancerous but not normal breast epithelial cells, Leronlimab may enhance the tumor specific activities of DDR-based treatments, allowing a reduction in dose of chemotherapy and radiation.

3. Leronlimab blocks breast cancer cell 3D-matrigel invasion

4. Leronlimab blocks breast cancer cell metastasis in a mouse lung metastasis model

5. Leronlimab enhances cell death induced by Doxorubicin