LTX-315: A first-in-class oncolytic peptide that reshapes the tumor microenvironment

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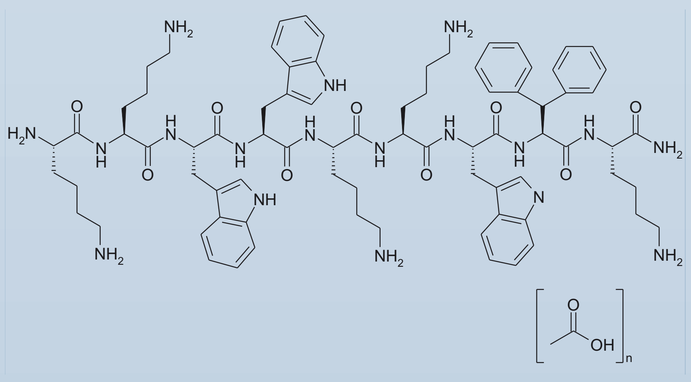
Background

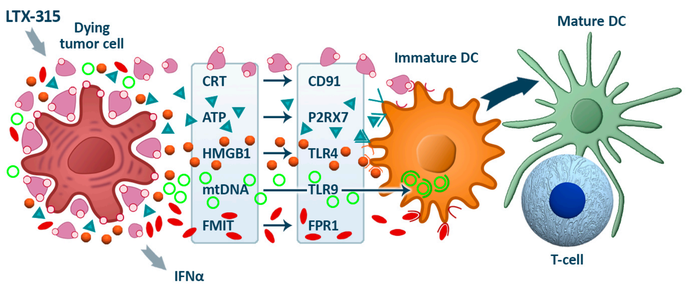
The oncolytic peptide LTX-315, which has been de novo designed based on structure-activity relationship studies of host-defense peptides, has the ability to kill human cancer cells and induce long-lasting anticancer immune response when injected locally into tumors established in immunocompetent murine models (1-3,11). The oncolytic effect of LTX-315 involves perturbation of the plasma membrane and the mitochondria with subsequent release of danger-associated molecular pattern molecules (DAMPs) such as ATP, Cytochrome C and HMGB1 (4-9). Furthermore, LTX-315 effectively disintegrates the cellular compartments with subsequent release of tumor antigens as demonstrated by a greater T-cell infiltration (TILs), TILs clonality and the number of clones with greater abundance in the tumor microenvironment. In experimental tumor models, LTX-315 exerts abscopal effects and reshapes the tumor microenvironment by decreasing the local abundance of immunosuppressive cells and by increasing the frequency of effector T-cells (9,10). LTX-315´s ability to convert immunogenically "cold" tumors to "hot" makes it ideal combination partner with other immunotherapies as confirmed in experimental tumors combining LTX-315 with immune checkpoint inhibitors and immunochemotherapy.

LTX-315

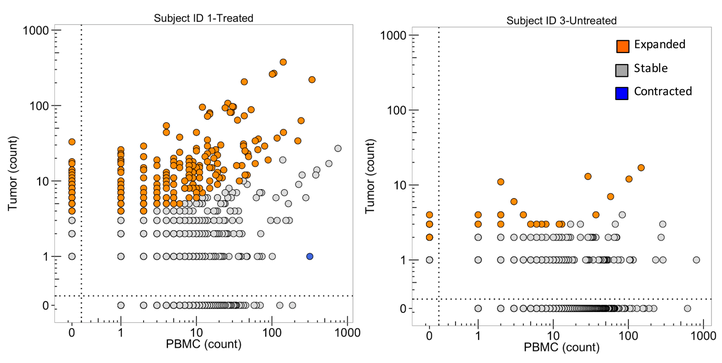


Mode of action

LTX-315 induces a unique type of immunogenic cell death

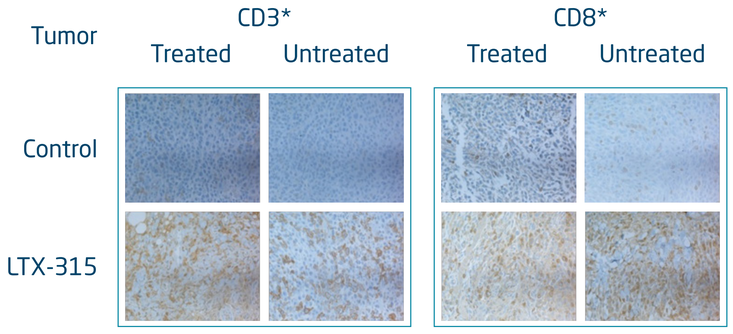


LTX-315 increases the number and diversity of T cell clones



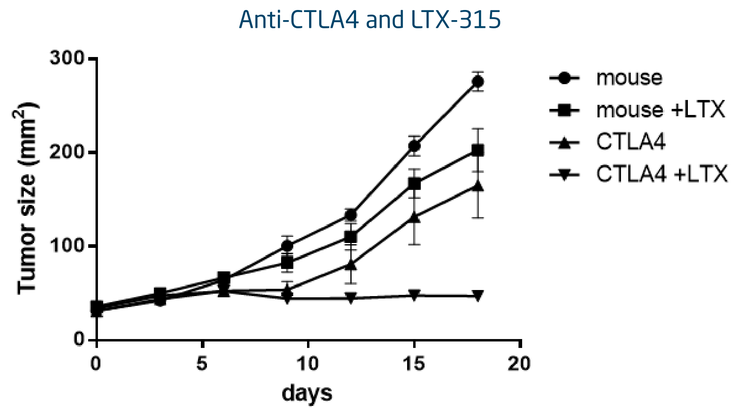
T cell clones in LTX-315-treated and control tumors (B-16 melanoma) were amplified and sequenced using the ImmunoSeq platform by Adaptive Biotech. Multiplex PCR was used to amplify the rearranged TCR3b sequences from sample DNA (VDJ region).

LTX-315 treatment leads to increased tumor infiltration of CD8+ T cells



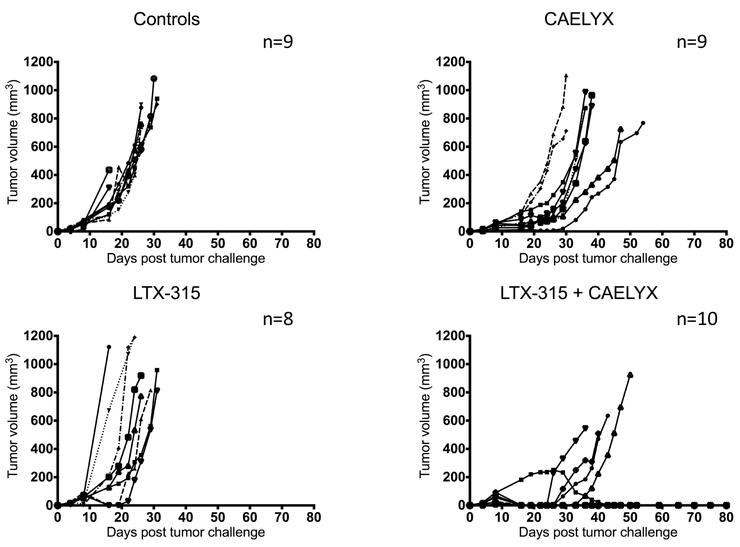
Treatment induces T-cell infiltration into both treated primary lesions but also in distal non-treated tumors (abscopal effect)

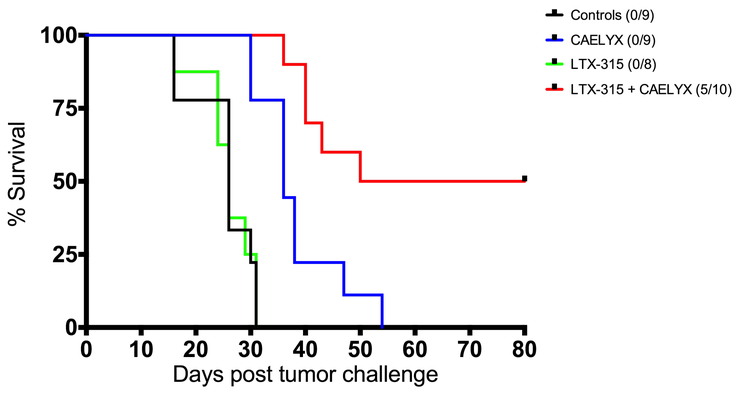
LTX-315 works in synergy with immune checkpoint therapy



LTX-315 treatment caused regressions in tumors that were resistant to anti-CTLA4. (Murine MCA205 sarcoma)

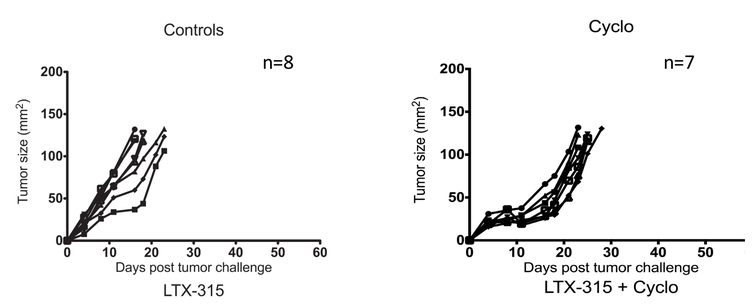
LTX-315 in combination with doxorubicin induces complete regression of orthotopic 4T1 mammary carcinomas

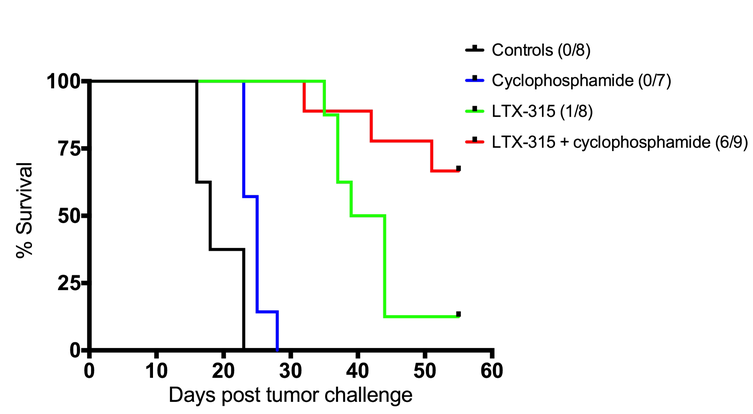




Tumor growth of orthotopically established 4T1 tumors in animals injected intratumorally with LTX-315 alone (1 mg/50 µl), intravenously with CAELYX alone (8mg/kg), or with LTX-315 in combination with CAELYX. CAELYX is liposomal doxorubicin.

LTX-315 in combination with cyclophosphamide induces complete regression of A20 B-cell lymphomas





Tumor growth of subcutaneously established A20 tumors in animals injected intratumorally with LTX-315 alone (1 mg/50 µl), intraperitoneally with cyclophosphamide alone (2mg/mouse), or with LTX-315 in combination with cyclophosphamide.

Conclusion

- LTX-315 shows an enhanced anticancer efficacy against A20 lymphomas and 4T1 breast carcinomas when combined with cyclophosphamide and doxorubicin, respectively.
- LTX-315 acts in synergy with checkpoint inhibition.
- The LTX-315 unique "release and reshape" properties make it a promising candidate for combination with several types of immunotherapies.
- LTX-315 is currently in clinical phase 1/2a studies.

References

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