Ethics Approval IRB exempted for case report with no patient-identifiable information
Consent N/A

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594 BT-001, AN ONCOLYTIC VACCINIA VIRUS ARMED WITH A TREG-DEPLETING HUMAN RECOMBINANT ANTI-CTLA4 ANTIBODY AND GM-CSF TO TARGET THE TUMOR MICROENVIRONMENT

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Background Checkpoint inhibitor antibodies have improved survival in a variety of cancers, however, a great unmet need remains since only a small fraction of patients responds. Reasons for lack of efficacy are believed to include lack of tumor infiltrating immune cells, a notion supported by improved efficacy observed following combined checkpoint blockade with tumor oncolytic virotherapy which promotes intratumoral T cell infiltration. Oncolytic vaccinia viruses (oVV) also allow genetic encoding of transgenes. This is of special interest for therapeutic proteins exhibiting toxicological limitation or pharmacokinetic issues. Here, BioInvent and Transgene present a potentially safe and more efficacious strategy to combine checkpoint inhibition in the context of oncolytic virotherapy.
Methods Using the F.I.R.S.T™ discovery platform we have isolated a human recombinant Treg-depleting antibody that has been vectorized alongside GM-CSF into the Invir.IO® oVV. This product named BT-001 consists of a Copenhagen double deleted vaccinia virus encoding the human CTLA4-specific antibody 4-E03 IgG1, which shows improved Treg-depletion compared with ipilimumab in a human PBMC-based NOG/SCID-transfer model. BT-001 also encodes GM-CSF, the cytokine expressed in clinically approved products. A surrogate murine mAb was vectorized into the same oVV (mBT-1) allowing for functional and mechanistic in vivo studies.
Results Our studies demonstrate that 4-E03 and GM-CSF were expressed as functional molecules after infection by BT-001 of human tumor cell lines in vitro. Moreover, following intratumoral administration in immune competent and immune deficient mice transplanted with mouse or human tumors, transgene expression was sustained at levels associated with receptor saturation for days to weeks. In contrast, and supporting the tumor-selective nature of oVV, blood concentrations of anti-CTLA4 mAb were lower compared to those observed following i.v. administration of therapeutic doses of mAb. The in vivo anti-tumor activity of mBT-1 was assessed in multiple syngeneic mouse tumor models including CT26, EMT6, A20 and C38. Murine surrogate mBT-1 conferred cures in the majority of challenged mice irrespective of tumor origin. The excellent anti-tumoral profile depends on anti-CTLA4 expression and could be boosted by co-administration of anti-PD-1 mAb. Intratumoral treatment with mBT-1 also induces abscopal anti-tumor responses and protects against tumor rechallenge demonstrating a long-lasting systemic anti-tumor activity.
Conclusions A clinical batch of BT-001 has been produced and toxicological evaluation is ongoing. Transgene and BioInvent have applied for a clinical trial targeting injectable superficial tumors. Here, the tumor-localized delivery of anti-CTLA4 may allow a better tolerated and more effective combination therapy with antibodies targeting the PD-1/PDL1 axis.

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595 ARMED MYXOMA VIRUS DEMONSTRATES EFFICACY IN SYNGENEIC TUMOR MODELS ALONE AND IN COMBINATION WITH IMMUNE CHECKPOINT INHIBITORS

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Background Oncolytic Viruses (OV) selectively replicate in and lyse tumor cells and provide stimulation to the immune system. This represents a promising therapeutic option for cancer patients that do not respond well to treatment with immune checkpoint inhibitors. Myxoma virus (MYXV) is a member of the Poxv family of double stranded DNA viruses. The natural host of MYXV is a subset of rabbits and hares, but MYXV can infect cancer cell lines of humans and other species. The genome of MYXV is relatively large and is amenable to engineering for expression of transgenes making it an excellent oncolytic virus for introduction of immunomodulatory proteins.
Methods Armed MYXV were tested for oncolytic activity and transgene production in syngeneic mouse cancer models in vitro and in vivo. In vivo models were further assessed for activity when in combination with immune checkpoint inhibitors and for immune mechanisms of action contributing to the efficacy of armed MYXV.
Results Armed MYXV demonstrated oncolytic activity, transgene production capability and in vivo activity following intratumoral and intravenous administration of armed myxoma viruses in murine cancer models. Additional combination therapy with clinically relevant immune checkpoint inhibitors is demonstrated.
Conclusions Armed Myxoma viruses present an efficacious novel oncolytic viral therapy with the ability to modulate immune responses in murine cancer models.
Ethics Approval Animal studies we approved by OncoMyx and the TD2 IACUC.

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596 ARMED MYXOMA VIRUS DEMONSTRATES THERAPEUTIC ACTIVITY IN XENOGRAFT MODELS

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Background Oncolytic Viruses (OV) selectively replicate in and lyse tumor cells and provide stimulation to the immune system. This represents a promising therapeutic option for cancer