BT-001, an oncolytic vaccinia virus armed with a Treg-depleting human recombinant anti-CTLA4 antibody and GM-CSF to target the tumor microenvironment

Monika Semmrich[1], Jean-Baptiste Marchand[2], Laetitia Fend[2], Matilda Rehn[1], Nathalie Silvestre[2], Linda Mårtensson[1], Johann Foloppe[2], Ingrid Teige[1], Eric Quéméneur[2] and Björn Frendeus[1]
[1] BioInvent International AB, Ideongatan 1, 22370 Lund, Sweden
[2] Transgene SA, 400 Blvd Gonthier d'Andernach, 67 405 Illkirch Graffenstaden, France

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.