ICAM-1 is highly expressed in NSCLC, melanoma and a subset of hepatocellular carcinoma and kidney cancer

ICAM-1-VC001 is highly effective in lymphoma and multiple myeloma models, superior to the benchmark ICAM-1-DXd

ICAM-1-VC001 has potent anti-tumor activities against melanoma, NCC and NSCLC models, and has repeatedly outperformed ICAM-1-DXd

Conclusions

ICAM-1-VC001 is a versatile novel topoisomerase I inhibitor-based ADC. It comprises a humanized anti-ICAM-1 antibody, which is conjugated with a novel topoisomerase I inhibitor via a cleavable linker at a DAR of about 8. In vivo, ICAM-1-VC001 demonstrated potent cytotoxicity against various hematologic and solid tumor cell lines with EC50s in the single-digit nanomolar range. It demonstrated high cytotoxicity even against cell lines that were insensitive to ICAM-1-DXd (DAR 8), the benchmark deruxtecan conjugate. Consistent with the in vitro results, ICAM-1-VC001 inhibited robust anti-tumor activity across a broad range of hematologic and solid tumor CDX models, including NSCLC, hepatocellular carcinoma, melanoma, lymphoma, and multiple myeloma. Administration of one or two doses of ICAM-1-VC001 at 5 mg/kg was sufficient to reduce tumor regression. In contrast, ICAM-1-DXd was not consistently effective in the tumor models tested. Although the negative control ADC (Isotype-VC001) exhibited significant activity in the in vitro cytotoxicity assay, it had minimal anti-tumor effect in vivo, consistent with that of isotype-DXd. These findings indicate that ICAM-1-VC001 enables target-mediated killing in vivo. Notably, in a repeat dose exploratory non-human primate safety study, the benchmark conjugate ICAM-1-DXd (DAR 8) was well tolerated at the highest dose of 41 mg/kg. These results indicate that targeting ICAM-1 with topoisomerase I ADC can be safe.

A NHP study with ICAM-1-VC001 is planned.

A novel topoisomerase I inhibitor-based anti-ICAM-1 antibody drug conjugate for the treatment of hematologic malignancies and solid tumors

Oi Kwan Wong, David Jackson, Lei Shi, Qi Fei, Xiaocheng Chen and Leonard Post

Virtuoso Therapeutics, Inc., San Mateo, California, USA

ICAM-1 is highly expressed in NSCLC, melanoma and a subset of hepatocellular carcinoma and kidney cancer. ICAM-1 is a transmembrane protein and a member of the immunoglobulin superfamily. ICAM-1 is involved in many processes of cancer cells including migration, cell-cell communication, and adhesion. Therefore, targeting ICAM-1, we developed a novel ICAM-1 antibody drug conjugate (ADC) comprising a humanized anti-ICAM-1 IgG1 antibody conjugated with a novel topoisomerase I inhibitor via a cleavable linker (VC001) at a drug-to-antibody ratio (DAR) of about 8. The antibody moiety of the ADC targets a unique epitope on ICAM-1 that is distant from its ligand binding domain. The ICAM-1 ADC, called ICAM-1-VC001, exhibited potent in vitro cytotoxicity on a range of hematologic and solid tumor cell lines with single-digit nanomolar EC50s. In preclinical studies, administration of one or two doses of ICAM-1-VC001 at 5 mg/kg was sufficient to reduce tumor regression in various cell line-derived xenograft (CDX) models, including lung and liver cancers. At all tested doses thus far, our topoisomerase I ADC, ICAM-1-VC001, has demonstrated at least comparable, if not superior, efficacy to ICAM-1-DXd, which is the same ICAM-1 antibody conjugated with the benchmark topoisomerase I inhibitor Linker payload deruxtecan. In addition, in a repeat dose exploratory non-human primate safety study, the benchmark conjugate ICAM-1-DXd (DAR 8) was well tolerated at the highest dose of 41 mg/kg. In conclusion, ICAM-1 is an appealing target for A NHP study to evaluate the safety of ICAM-1-VC001 is planned.

ICAM-1 is a transmembrane protein and a member of the immunoglobulin superfamily. ICAM-1 is involved in many processes of cancer cells including migration, cell-cell communication, and adhesion. Therefore, targeting ICAM-1, we developed a novel ICAM-1 antibody drug conjugate (ADC) comprising a humanized anti-ICAM-1 IgG1 antibody conjugated with a novel topoisomerase I inhibitor via a cleavable linker (VC001) at a drug-to-antibody ratio (DAR) of about 8. The antibody moiety of the ADC targets a unique epitope on ICAM-1 that is distant from its ligand binding domain. The ICAM-1 ADC, called ICAM-1-VC001, exhibited potent in vitro cytotoxicity on a range of hematologic and solid tumor cell lines with single-digit nanomolar EC50s. In preclinical studies, administration of one or two doses of ICAM-1-VC001 at 5 mg/kg was sufficient to reduce tumor regression in various cell line-derived xenograft (CDX) models, including lung and liver cancers. At all tested doses thus far, our topoisomerase I ADC, ICAM-1-VC001, has demonstrated at least comparable, if not superior, efficacy to ICAM-1-DXd, which is the same ICAM-1 antibody conjugated with the benchmark topoisomerase I inhibitor Linker payload deruxtecan. In addition, in a repeat dose exploratory non-human primate safety study, the benchmark conjugate ICAM-1-DXd (DAR 8) was well tolerated at the highest dose of 41 mg/kg. In conclusion, ICAM-1 is an appealing target for A NHP study to evaluate the safety of ICAM-1-VC001 is planned.