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**AN ASSESSMENT OF ROR1 EXPRESSION ACROSS TUMOR TISSUE AND THE INVESTIGATION OF A ROR1-TARGETED T CELL ENGAGER AS A THERAPEUTIC STRATEGY TO TARGET ROR1 POSITIVE TUMORS**

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**Background** Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is expressed on a variety of difficult to treat solid and hematological malignancies. Several therapeutic molecules targeting ROR1 are currently in clinical studies, including antibody-drug conjugates (ADCs), chimeric antigen receptor engineered T cells (CARTs), as well as a bispecific T cell engagers (TCEs). For the therapy of ROR1 expressing tumors, we engineered a T cell engager (TCE) with prolonged half-life to support convenient administration schemes. We have profiled the expression pattern of ROR1 in tumors and investigated the ability of our ROR1 TCE to impact tumor growth.

**Methods** An in-situ hybridisation assay for detection of ROR1 transcript in paraffin-embedded human tumor sections was developed. Tissue microarrays from tumors of solid organ and haematological origin were screened for ROR1 transcript and expression was quantified by pathologist assessment. In vitro and in vivo assessment of cytotoxic activity and T cell activation of an anti-ROR1 TCE was performed using tumor cells with varying expression levels of ROR1.

**Results** ISH analysis of ROR1 transcript expression across tumor indications demonstrated expression in tumors of both solid and haematological origin. In particular, samples from Non-Hodgkin's lymphoma patients such as DLBCL and FL had a high prevalence of ROR1 transcript expression. Additionally, gynaecological cancers showed a high prevalence of ROR1 expression.

In vitro profiling of an anti-ROR1 TCE demonstrated sub-nM potency to elicit cytotoxicity of ROR1-positive tumor cells of various origin. T cell activation correlated with cytotoxicity and both events were ROR1-dependent.

In vivo profiling of the anti-ROR1 TCE demonstrated tumor growth inhibition of ROR1 positive haematological and solid tumors.

**Conclusions** A novel ROR1 ISH assay was established and used to identify ROR1 positive tumor tissue and quantify ROR1 expression levels as well as prevalence of ROR1 expression within tumor types. A ROR1 TCE was potent and rapid in its ability to induce cytolysis of ROR1 positive tumors in vitro and in vivo, correlating with the expression profile of ROR1 across tumor types.

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