Preclinical anti-tumorigenic evaluation of AXL targeting antibody-drug-conjugate in an adenoid cystic carcinoma cell line xenograft model

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ABSTRACT

Here we present data demonstrating that ADCT targeting human AXL carrying the payload PL1601 (Fig. 1), a potent pyrrolobenzodiazepine dimer cytotoxin with a cleavable linker (1).

METHODS AND MATERIALS

Cell line: MDA-ACC-01 (ACC-01) cell line was obtained from the University of Texas MD-Anderson Cancer Center (3).

Cell surface AXL validation: ACC-01 cells were labelled with biotin for 30 min with Sulfo-NHS-LC-Biotin (ThermoFisher Scientific). Protein extracts were then prepared and submitted to immunoprecipitation with either streptavidin-agarose or AXL antibody (C89E7, Cell Signaling Technology). Immunoprecipitated samples were then resolved in SDS-PAGE and processed for immunoblotting with anti-AXL (C89E7) or streptavidin-agarose conjugate.

ADCT-601 study in ACC-01 tumor xenograft: Generation of subcutaneous ACC-01 tumor xenograft in immunodeficient (NSG) mice has been previously described (4). Briefly, mice with tumor volume averaging ~ 200-300 mm³ were randomized into different groups and treated with vehicle (saline) and a single dosing of either a non-binding control isotype B12-PL1601 (0.5 mg/kg) or ADCT-601 (0.5 and 1.0 mg/kg) intravenously. In vivo experiments were performed in an animal facility approved by the UCSF IACUC protocol.

REFERENCES


SUMMARY

• ACC-01 cells express high cell surface AXL.
• ADCT-601 treatment with either 0.5 mg/kg or 1.0 mg/kg resulted in complete response (CR) for all tumor implants.
• Treating the vehicle-treated group with ADCT-601 (1.0 mg/kg) at day 14 strikingly led to tumor shrinkage and eradication in all but one case, thus reaffirming the drug’s efficacy.

CONCLUSIONS

These results substantiate that ADCT-601 is an effective drug with significant anti-tumor activity in our ACC preclinical models and is worthy of additional investigation to determine its translational potential.

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BACKGROUND AND OBJECTIVE

• AXL expression is upregulated in ACC and ADCT-601 shows significant anti-tumor activity in an ACC PDX model (2).

• The goal of this study is to corroborate the anti-tumorigenic effects of ADCT-601 using high AXL expressing ACC-01 cell line tumor model.

RESULTS

Table I. Summary of drug response. Note that vehicle group were challenged with ADCT-601 at day 14. CR: complete response; PR: partial response; SD/PD: stable disease/progression of disease.

Figure 1. Structure of ADCT-601.

Figure 2. Validation of high cell surface expression of AXL in ACC-01 cell line. ACC-01 cells labelled with biotin and the lysates were immunoprecipitated with either streptavidin-agarose (A) or AXL antibody (B) and analysed with Western blotting as indicated. In B, streptavidin-HRP membrane was stripped and re-probed with anti-AXL (bottom panel).

Figure 3. ADCT-601 significantly inhibits ACC-01 tumor growth. (A) Anti-tumor effects of vehicle treated, control B12-PL1601 or ADCT-601 in high AXL expressing ACC-01 cells. Note that vehicle group were challenged with ADCT-601 (1.0 mg/kg) at day 14 (red arrows) (B), Body weight changes of tumor-bearing mice treated with the vehicle, control B12-PL1601 or ADCT-601.

Figure 4. Summary of drug response. Note that vehicle group were challenged with ADCT-601 at day 14. CR: complete response; PR: partial response; SD/PD: stable disease/progression of disease.