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

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ABSTRACT

- Adenoid cystic carcinoma (ACC) is a rare cancer of salivary gland origin.
- A major challenge in managing patients with ACC is the lack of clinically approved drugs to successfully treat advanced recurrent/metastatic disease.
- AXL is a cell surface tyrosine kinase receptor belonging to TAM family. Overexpression and activation of AXL has been associated with poor prognosis and is implicated in conferring resistance to therapies in solid tumors.
- Here we present data demonstrating that AXL targeting antibody-drug-conjugate readily eradicated tumor in an ACC-01 tumor xenograft model.

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BACKGROUND AND OBJECTIVE

- ADCT-601 (mipasetamab uzoptirine) is an antibody-drug conjugate targeting human AXL carrying the payload PL1601 (Fig. 1), a potent pyrrolobenzodiazepine dimer cytotoxin with a cleavable linker (1).

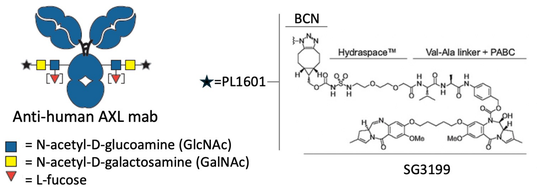

Figure 1. Structure of ADCT-601. Adapted from *Zammarchi, F. et. al.* (1). ADCT-601 is a proprietary of *ADC Therapeutics*.

- 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.

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 subjected 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-HRP conjugate.

ADCT-601 study in ACC-01 tumor xenograft: Generation of sub-cutaneous ACC-01 tumor xenograft in immunodeficient (NSG) mice has been previously described (4). Briefly, mice with tumor volume averaging ~ 200-300 mm^3 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.

RESULTS

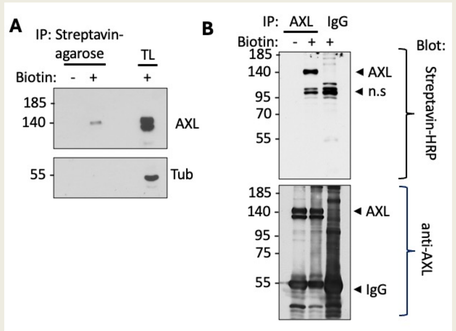

Figure 2. Validation of high cell-surface expression of AXL in ACC-01 cell line. ACC-01 cells labelled with biotin and the lysates were immunoprecipitated with either streptavidin agarose (**A**) or AXL antibody (**B**) and analyzed by Western blotting as indicated. In **B**, streptavidin-HRP membrane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

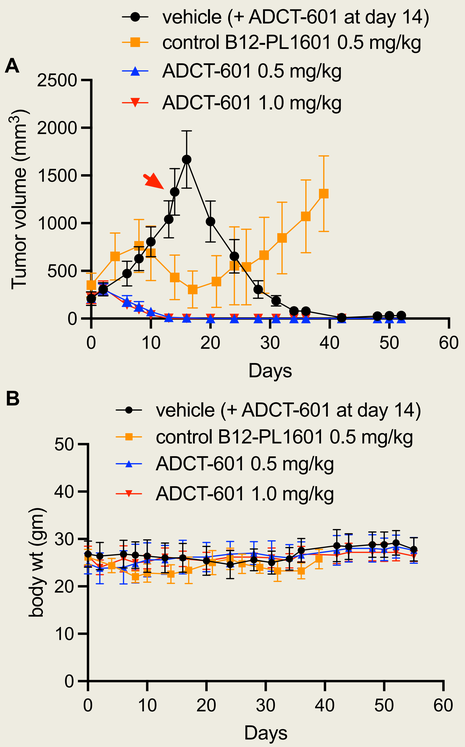

Figure 3. ADCT-601 significantly inhibits ACC-01 tumor growth. (**A**),anti-tumor effects of vehicle treated, control B12-PL1601 or ADCT-601 in high AXL expressing ACC-01 cells. Note that vehicle group were challenged with ADCT 601 (1.0 mg/kg) at day 14 (red arrow). (**B**), Body weight changes of tumor-bearing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

ACC-01 cells xenograft	SD/PD	PR	CR
Vehicle-saline* (n=7)	0	1	6
Control-IgG (B12-PL601) (0.5 mg/kg) (n=7)	7	0	0
ADCT-601 (0.5 mg/kg) (n=9)	0	0	9
ADCT-601 (1.0 mg/kg) (n=7)	0	0	7

Table I. Summary of drug response. Note that vehicle group were challenged with ADCT 601 at day 14. CR: complete response, PR: partial response (≧50% tumor shrinkage), SD/PD: stable disease/progression of disease.

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.

REFERENCES

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