

# Ultrasound-induced cavitation enhances therapeutic efficacy of AXL-targeting ADC leading to improved survival in a human xenograft model of renal cancer

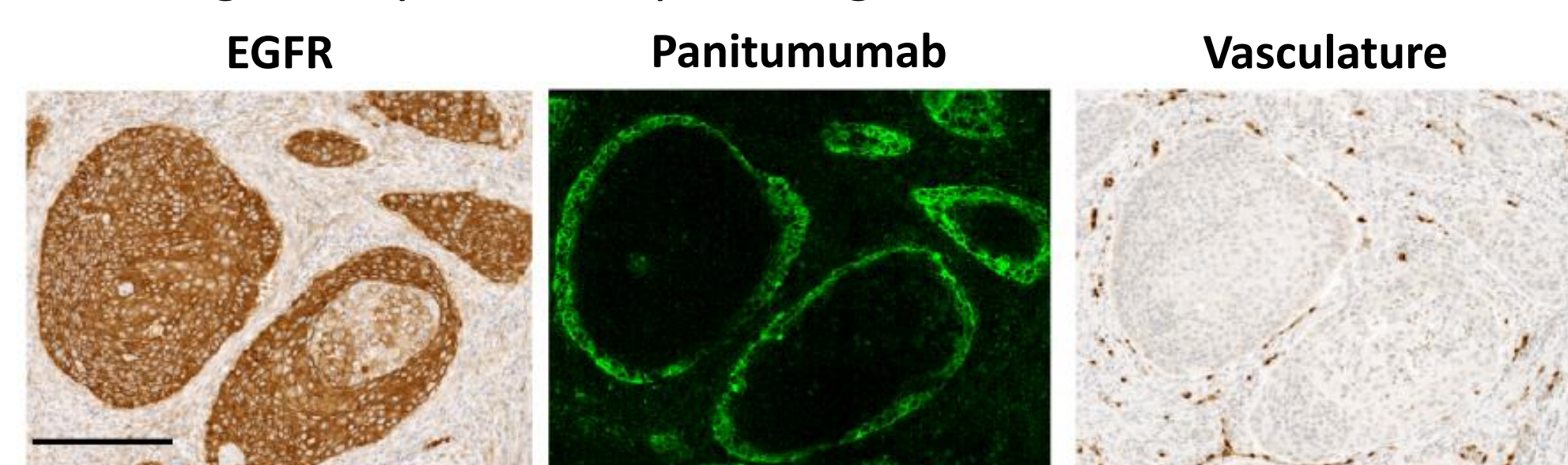
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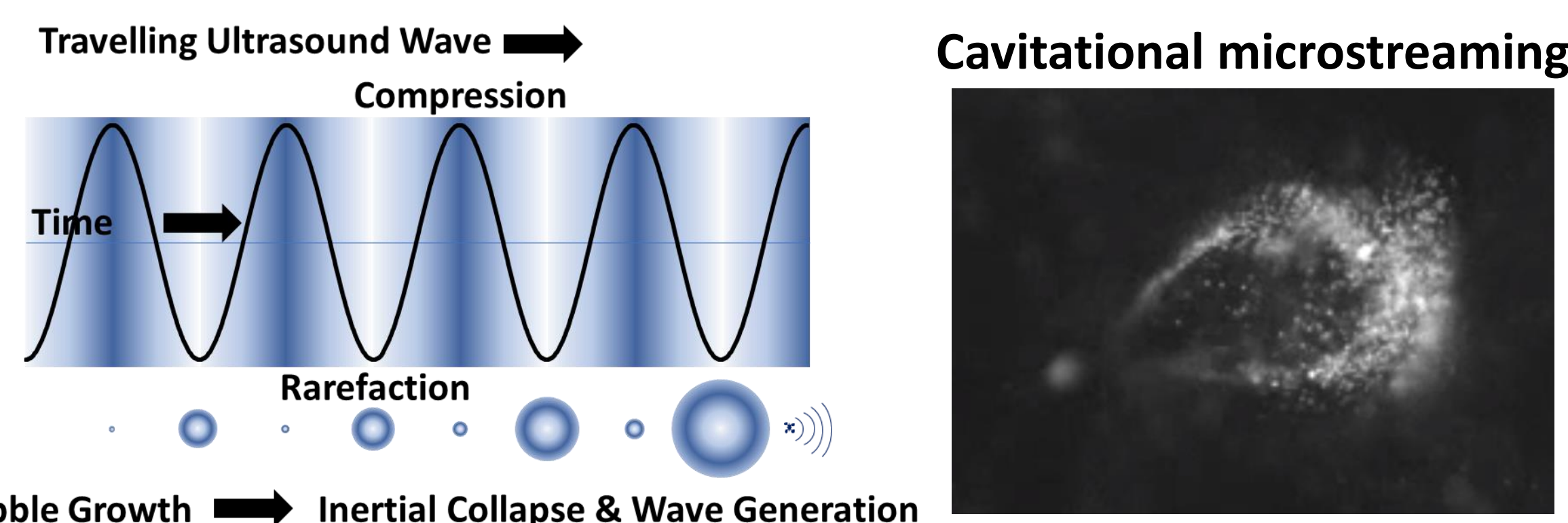
## Background and Hypothesis

- Antibody-drug conjugates (ADCs): class of anti-tumor agents that combine the targeting specificity of monoclonal antibodies (mAbs) with the cell killing ability of powerful cytotoxic molecules.
- Poor penetration of drugs into solid tumors, including mAbs, is a well-recognized barrier to effective therapy as this strongly limits the number of tumor cells targeted by the therapeutic agent.



Lu G, et al. Clin Cancer Res. 2020

- A novel non-invasive approach to tackle this problem is SonoTran. This technology enhances drug delivery thanks to ultrasound-induced inertial cavitation from sub-micron bubbles co-infused with the drug.



- The purpose of this study was to test a single dose of mipasetamab uzoptirine (ADCT-601), an ADC targeting the AXL protein, in combination with SonoTran in a preclinical mouse model of renal cancer.

## Methods

- Mice implanted with SN12C human renal cancer cells were divided into cohorts when tumors reached an average size of 150 mm<sup>3</sup>:
  - PBS (vehicle control)
  - B12-PL1601 (control ADC) at 0.3 mg/kg ± SonoTran
  - ADCT-601 at 0.3 mg/kg (suboptimal dose) ± SonoTran
  - ADCT-601 at 1 mg/kg (efficacious dose).
- Bubble-stabilizing particles and drug agent were administered intravenously just before ultrasound application from the OxSonics SonoTran System.
- Ultrasound parameters: fc=0.5MHz; 8000cycles; PRF=0.5Hz; PRFP=1-2.9MPa variable. Ultrasound amplitude was set according to the cavitation monitoring method (passive acoustic mapping [PAM]) to be within 0.1–0.5 nJ/pulse for 10 minutes of treatment.

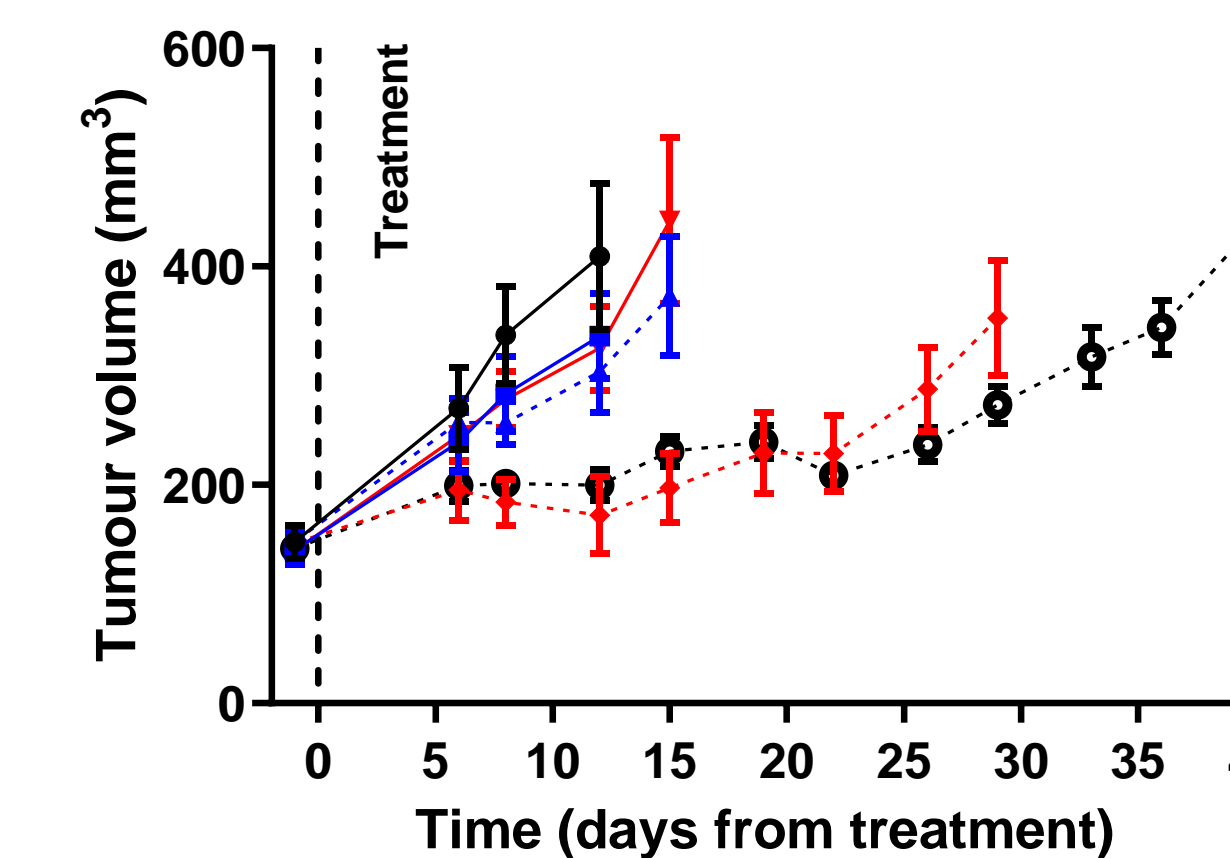
## Results

- Treatments (antibody alone or with SonoTran) were well tolerated.
- Following treatment, 2 groups (ADCT-601 at 1 mg/kg and ADCT-601 at 0.3 mg/kg + SonoTran) showed significant tumor growth delay and significant improvement in survival when compared to all other groups.
- No significant difference between the high and the low ADCT-601 dose with SonoTran was observed, indicating that the combination enhanced potency by 3.3-fold.

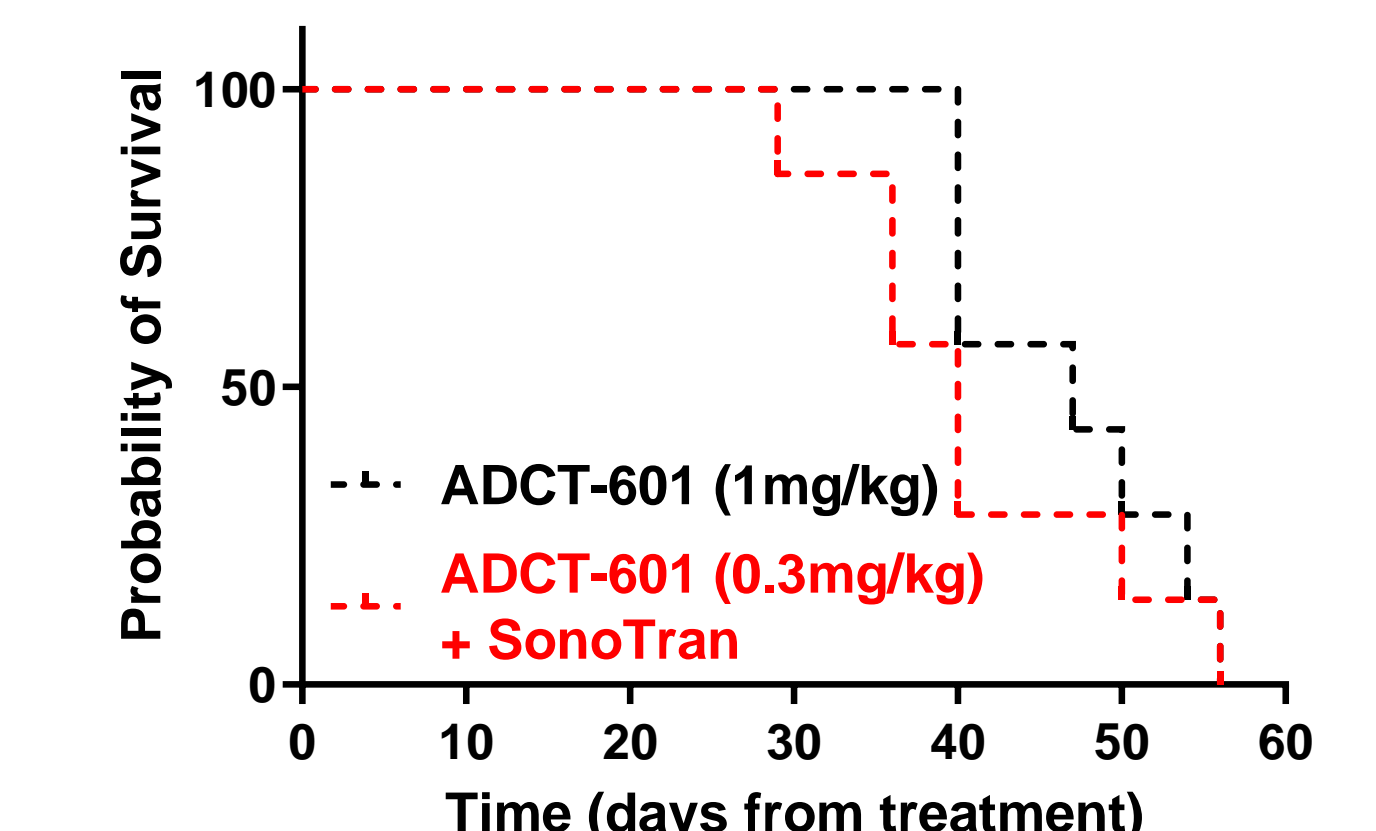
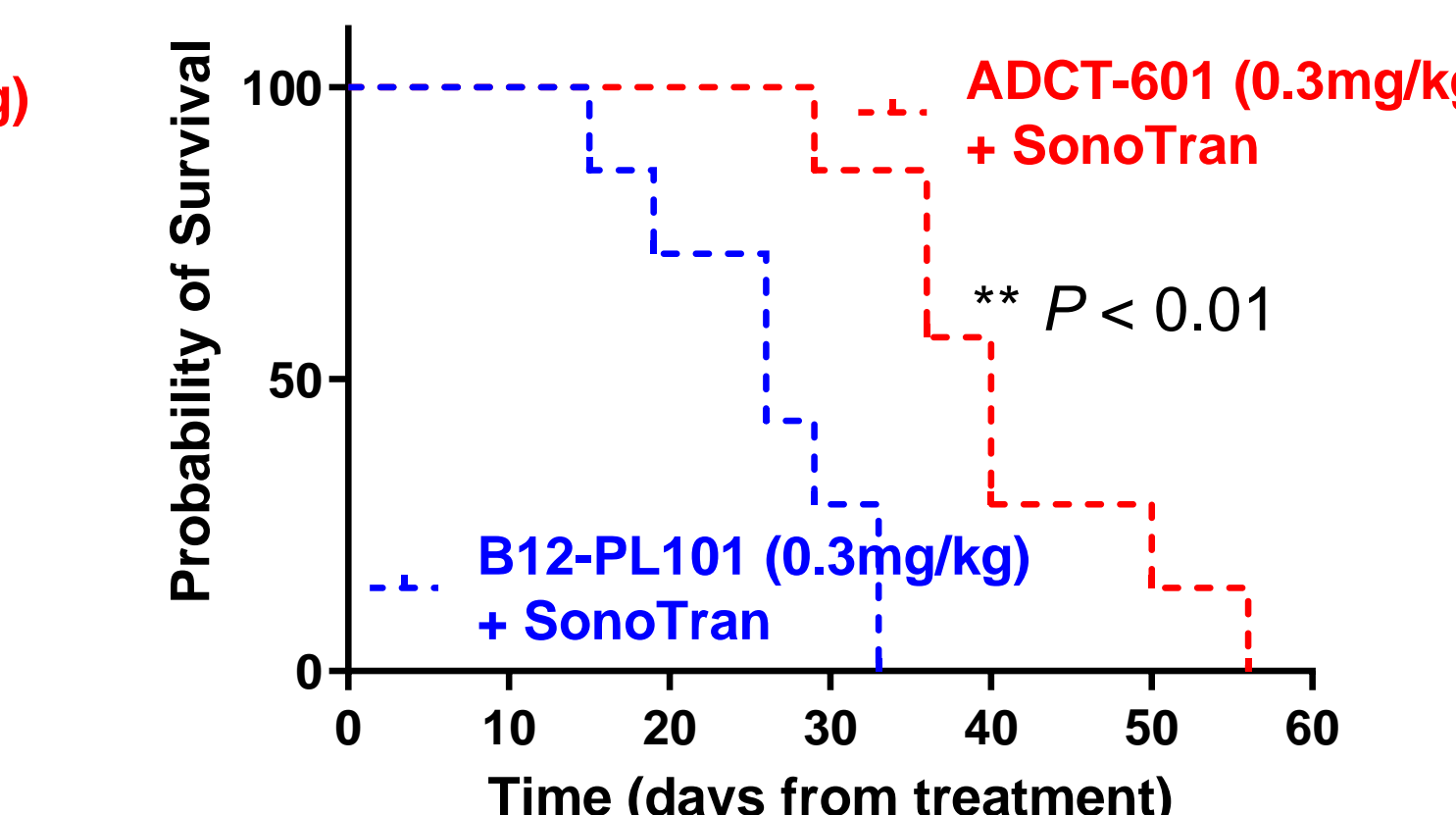
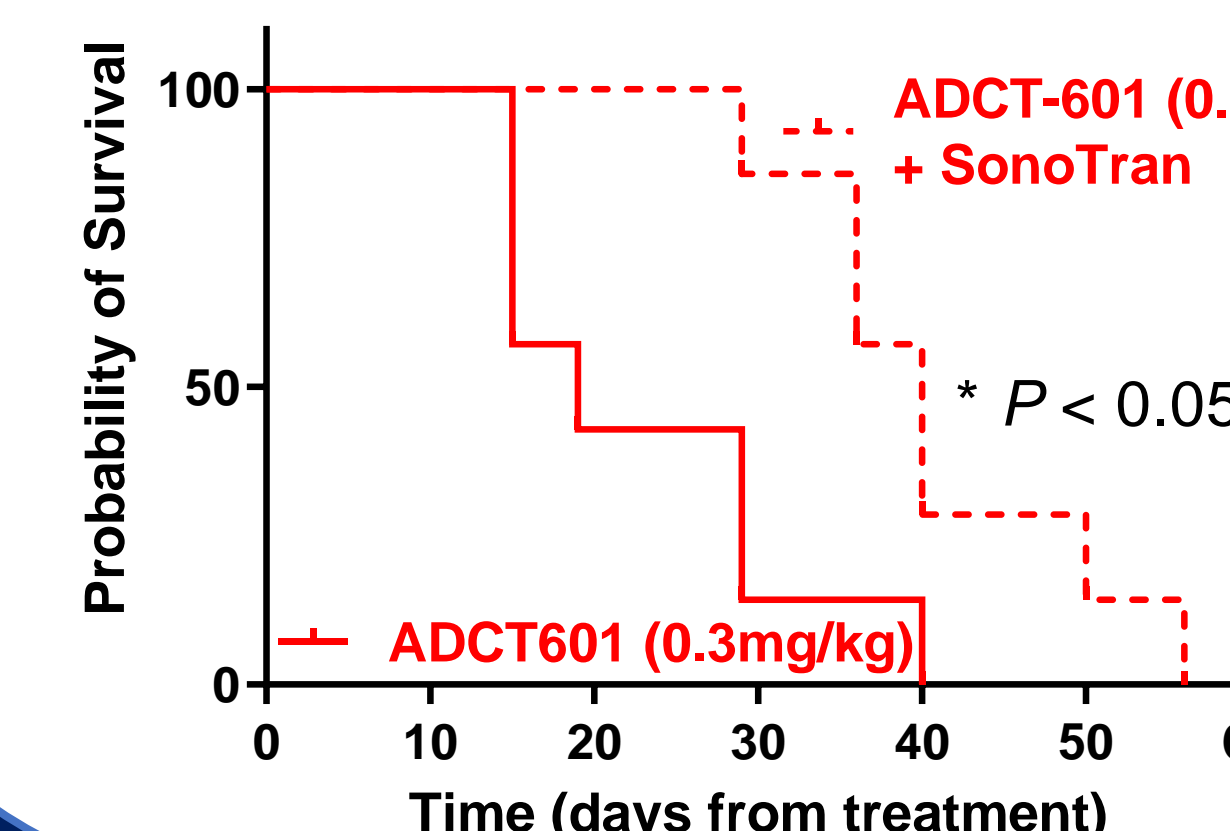
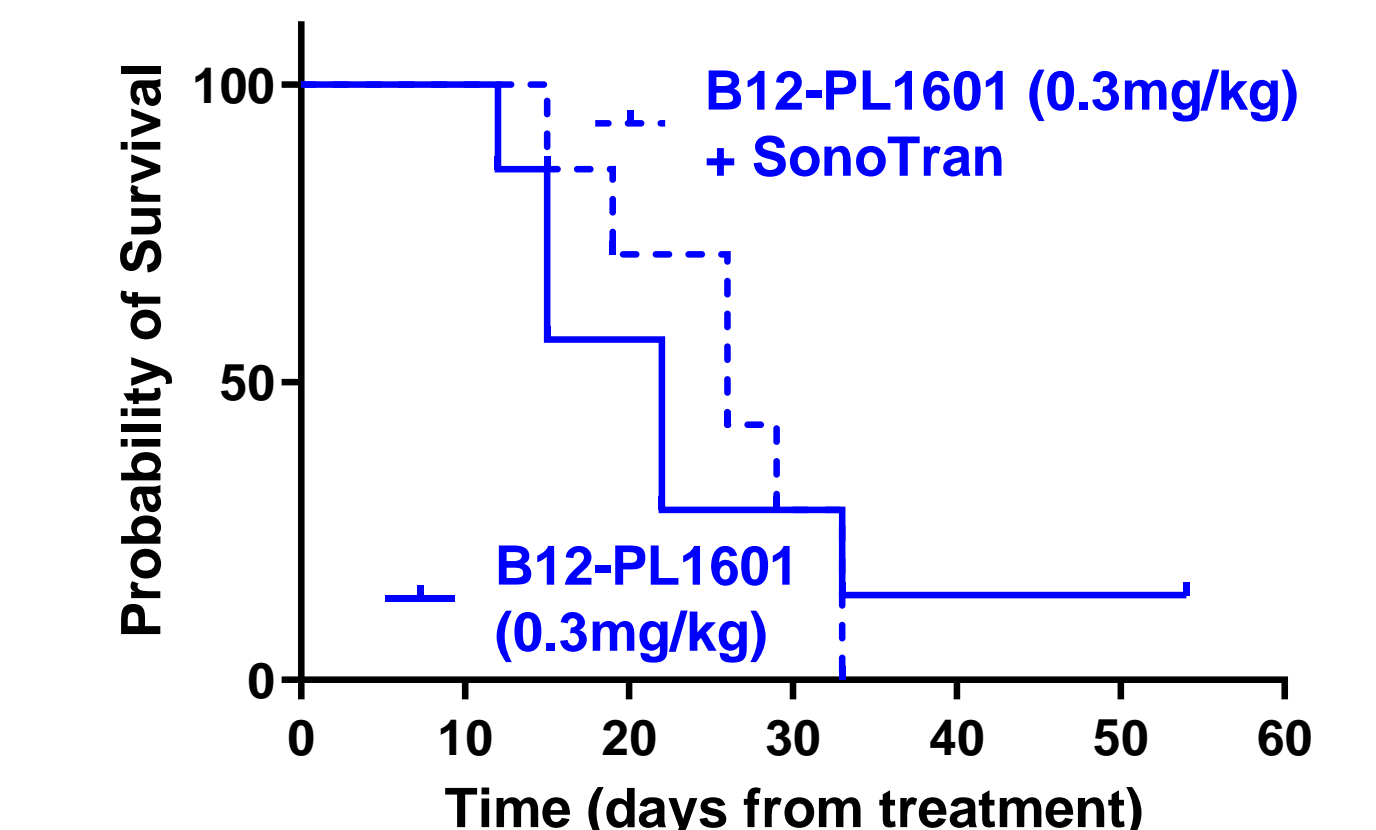
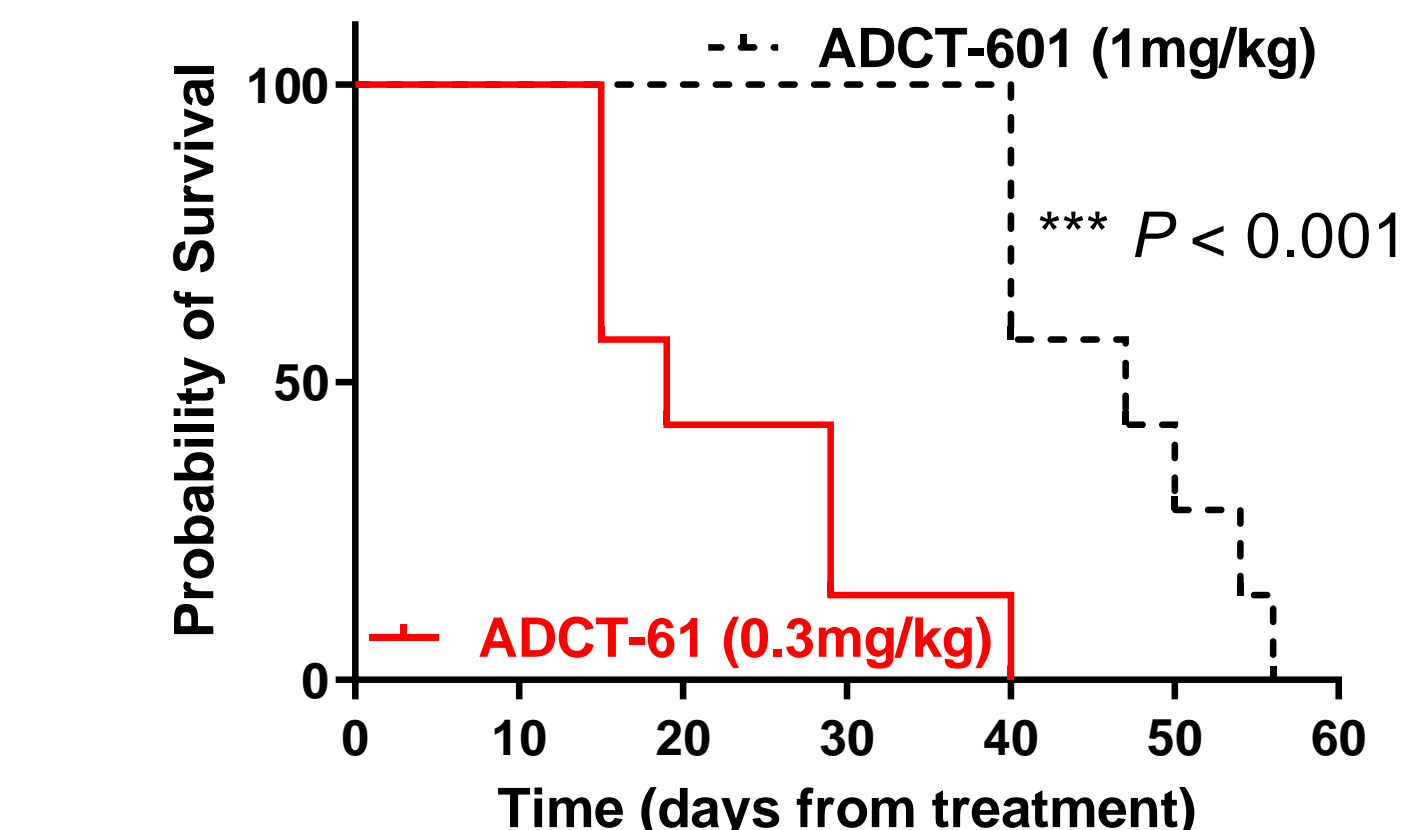
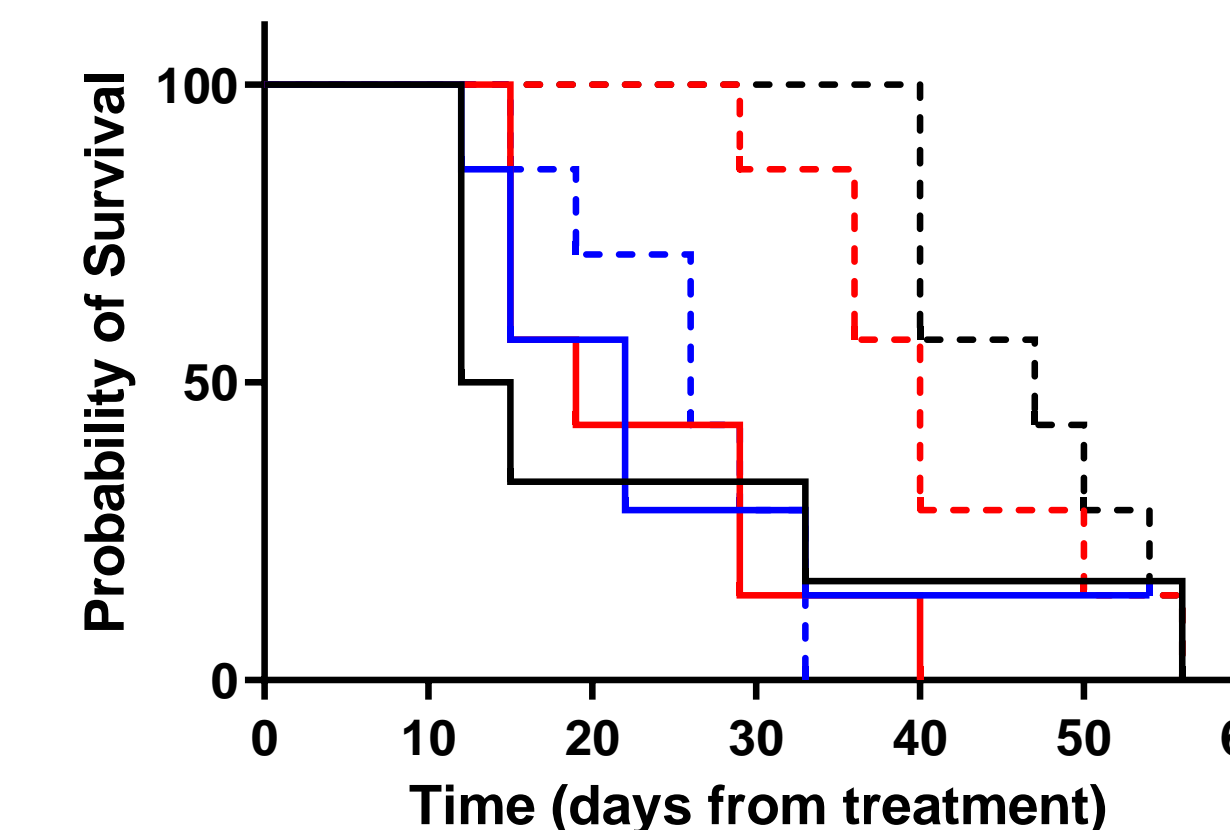
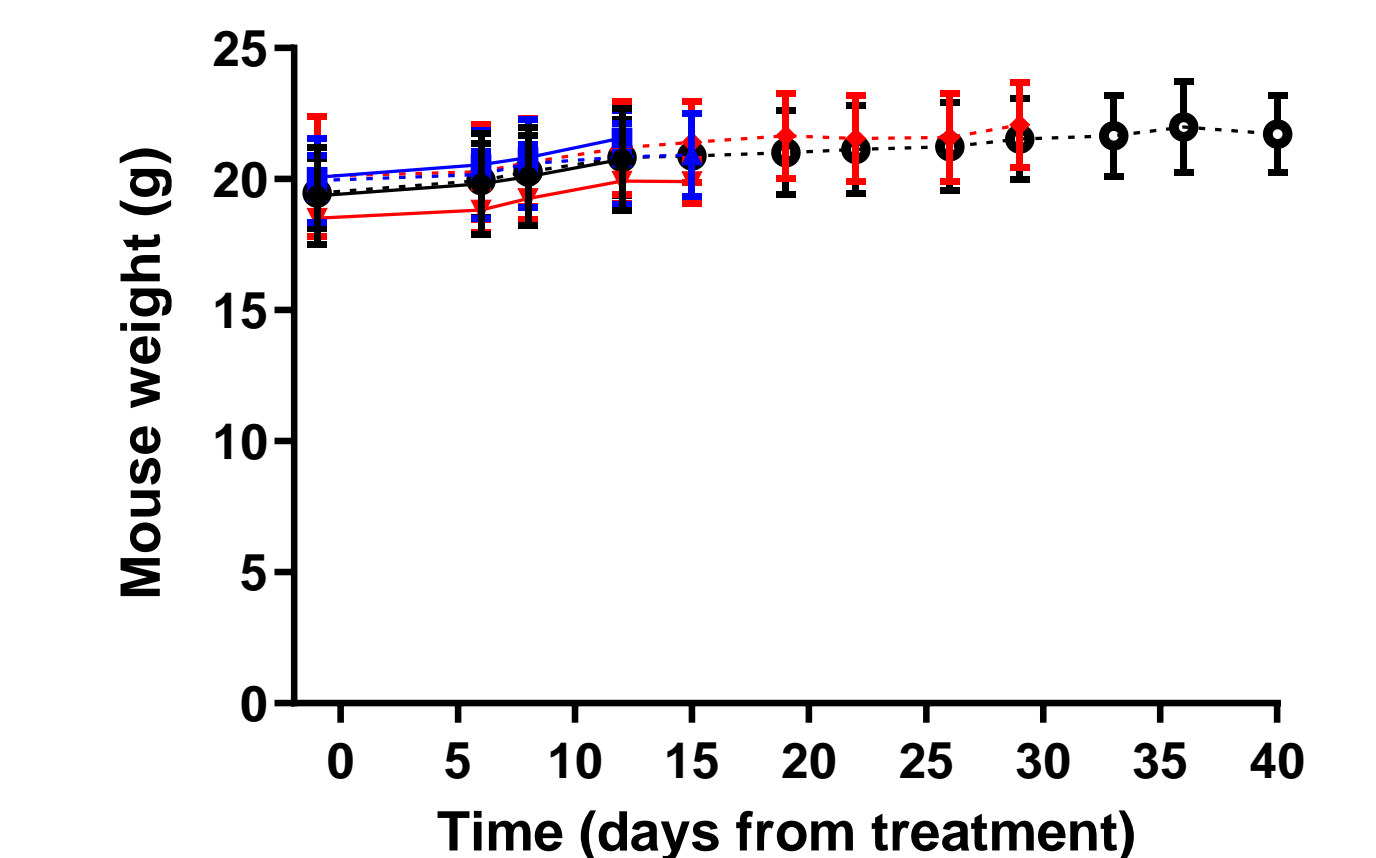
## Conclusions

- Cavitation-enhanced delivery of ADCT-601 has a strong effect on xenograft tumor growth leading to a significant increase in survival.
- SonoTran offers the opportunity to both increase the efficacy of ADC assets with acceptable toxicity profile or to reduce the administered dose while preserving therapeutic efficacy.

## Experimental Data

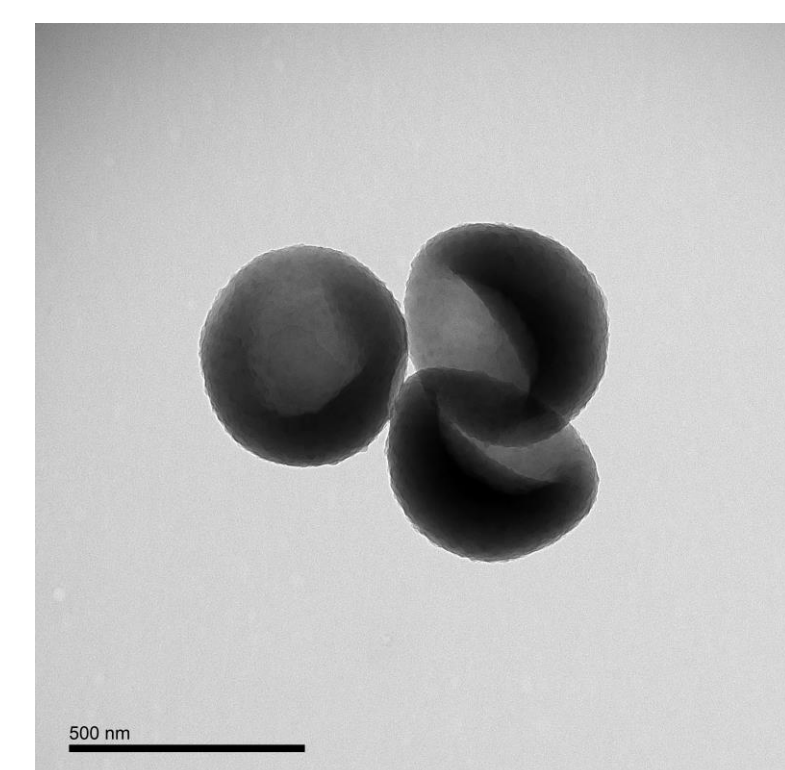


Treatment Group	Median survival (days)
PBS	13.5 days
B12-PL1601	22 days
B12-PL1601 + SonoTran	26 days
ADCT-601	19 days
ADCT-601 + SonoTran	40 days
ADCT-601 (1mg/kg)	47 days



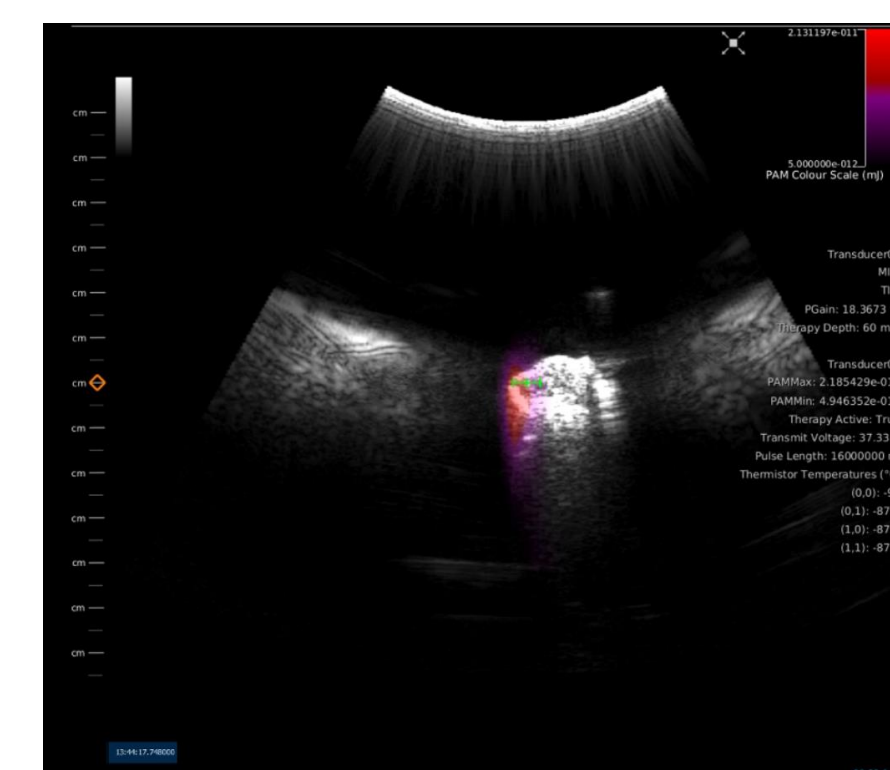
## SonoTran Background

### Bubble-stabilizing particles



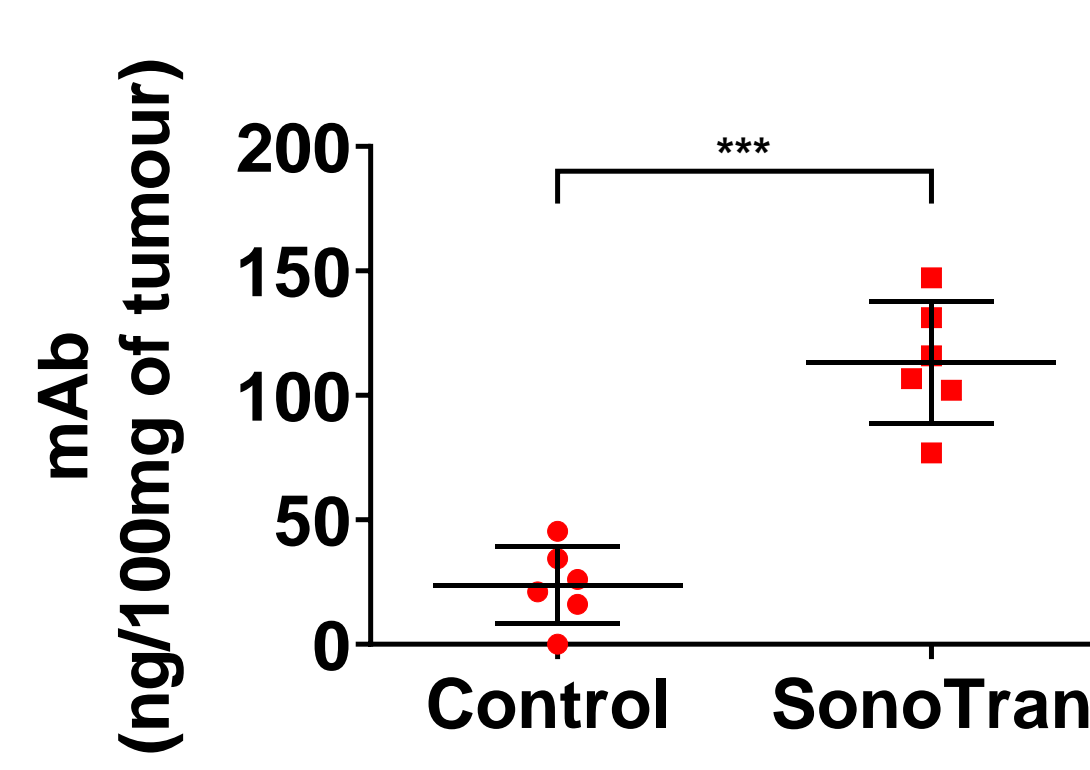
SonoTran Particles

### Cavitation live detection and targeting



Cavitation signal (in color scale) quantified by PAM and overlaid on B-mode imaging

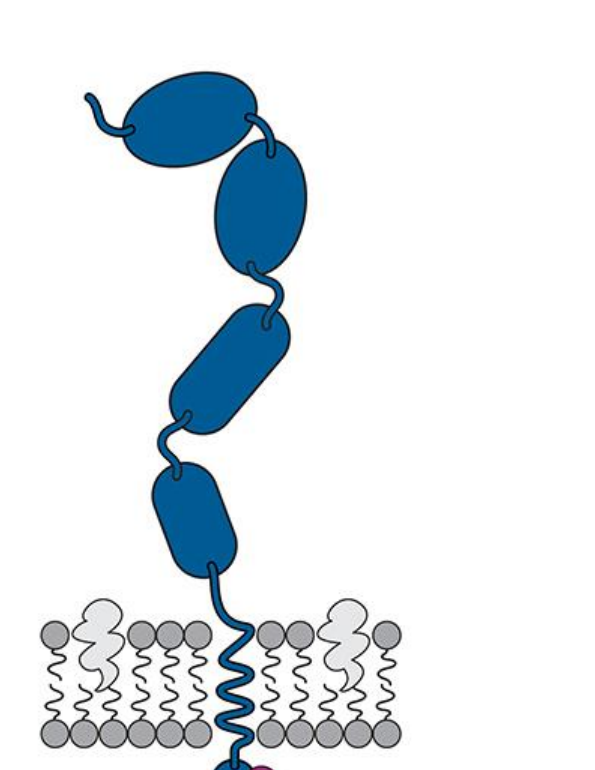
### Drug delivery



Monoclonal antibody (mAb) delivery in an experimental mouse model ± SonoTran (OxSonics Therapeutics unpublished data)

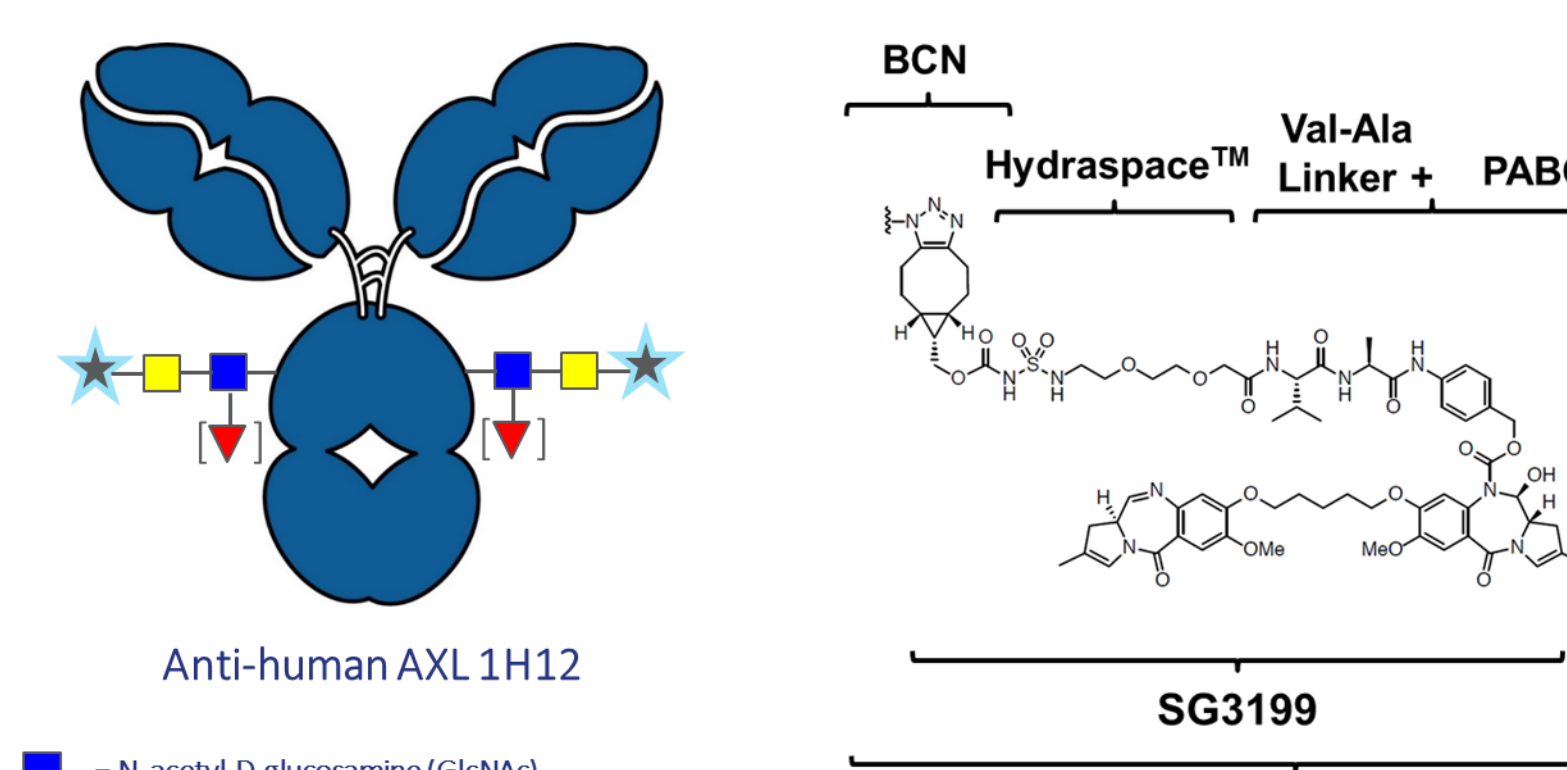
## ADCT-601 Background

### AXL



Tyrosine kinases over-expressed in various tumor types

### ADCT-601



Zammarchi F, et al. Mol Cancer Ther. 2022



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