In vivo results of AGX101, a TM4SF1-directed tubulin inhibitor conjugate, in combination with immune checkpoint inhibitors

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Abstract

Introduction

TM4SF1 (Transmembrane-4 L-Six-Family-Member-1) is an endothelial marker with critical roles in angiogenesis[1], as well as a tumor cell antigen that contributes significantly to invasion and metastasis[2]. TM4SF1 is upregulated 20-fold in angiogenic tumor vascular endothelium compared to normal vasculature endothelium and exhibits a unique nuclear internalization pathway[3].

AGX101 is a novel tubulin inhibitor conjugate specifically directed against TM4SF1, delivering a potent maytansinoid payload directly to the nucleus[1,3,4] of cells within the tumor microenvironment resulting in three mechanisms of action (MoAs): (1) activation of tumor immune surveillance, (2) tumor blood supply deprivation, and (3) direct tumor cell killing.

Methods

TM4SF1 expression was assessed using immunohistochemistry. Safety and pharmacokinetics of AGX101 were evaluated in non-human primates (NHP), with escalating doses to determine the highest non-severely toxic dose (HNSTD).

Efficacy studies were also conducted in mouse models, enabling assessment of the minimum effective dose (MED) needed to engage each of the three MoAs. The combination of HNSTD and MED enables calculation of a therapeutic index (TI). The potential for synergy with immune checkpoint inhibitors (ICIs) was also investigated.

Results

Notable cancers with high TM4SF1 scoring intensity include lung cancer, kidney cancer, ovarian cancer, GI cancers, and breast cancer. In NHP, AGX101 exhibited a favorable safety profile.

In preclinical efficacy studies, monotherapy demonstrated robust efficacy through each of the three MoAs in mouse syngeneic models including CT26 colon carcinoma and human tumor xenograft models including MIA PaCa-2 pancreatic cancer. Measured by exposure, TI was large. In syngeneic mouse models the effects of ICIs were potentiated by the AGX101 murine surrogate AGXB01, suggesting potential synergy. High response rates (RR) were achieved including CT26 with 71% RR for AGXB01+anti-CTLA-4 antibody vs 13% for anti-CTLA-4 alone; Renca mouse renal cancer model with 80% RR for AGXB01+anti-CTLA-4 antibody vs 20% for anti-CTLA-4 alone. In B16F10 mouse melanoma, a non-responsive model, AGXB01+ anti-PD-1 antibody or anti-CTLA-4 antibody doubled survival time vs either monotherapy of AGXB01 or anti-PD-1 antibody or anti-CTLA-4 antibody. In rechallenge experiments, 38 of 39 mice that had been rechallenged after tumor-free responses successfully eradicated new tumors without drug retreatment, demonstrating a durable immune response.

Conclusion

AGX101 represents a promising new approach in cancer therapy. The preclinical data suggest that AGX101 could provide a significant therapeutic benefit by novel and differentiated mechanisms of action, namely selectively targeting the tumor vasculature and potentiating ICIs. Further clinical development of AGX101 is ongoing.

References

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3. Sciuto TE, Merley A, Lin CI, Richardson D, Liu Y, Li D, Dvorak AM, Dvorak HF, Jaminet SC. Intracellular distribution of TM4SF1 and internalization of TM4SF1-antibody complex in vascular endothelial cells. Biochem Biophys Res Commun. 2015; 465(3):338-43. PMID: 26241677
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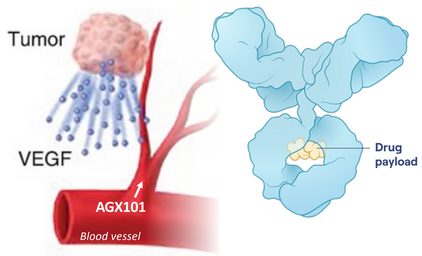
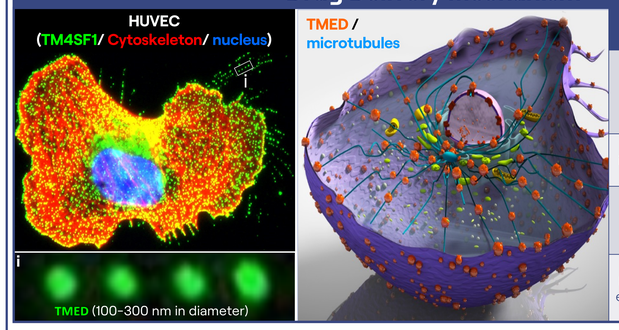
Blood vessel targeting as the primary action of AGX101



- **Approved anti-angiogenic drugs are antibody drugs that inhibit VEGF-A stimulation of VEGFR2 to slow down tumor growth.**
  - Drugs need to reach the tumor microenvironment to prevent this stimulation.
- **AGX101 targets tumor vessels, depriving tumors of nutrients and oxygen to induce ischemia and a coagulative necrosis.**
- **AGX101 also targets tumor cells as TM4SF1 is a tumor cell associated antigen.**
  - Internalization of AGX101 leads to intracellular payload release for cytotoxicity.

Drug Delivery Mechanism



Conventional ADC	TM4SF1-directed ADC
Internalization starts with membrane vesicles (60–120 nm in diameter)	Internalization starts with TMED microdomains (100–300 nm in diameter)
ADCs internalize into endosomes-lysosomes	ADCs internalize into the nucleus via microtubules
Antibodies are degraded in lysosomes	Antibodies are degraded by the nuclear proteasome
Payloads need to escape lysosomes	Payloads have direct access to nucleus and cytosol

AGX101 MOA: TM4SF1-enriched microdomains (TMED) internalize from the cell surface along microtubules. TMEDs are transported along microtubules to the MTOC (microtubule organization center) and then enter the nucleus via nuclear pores. AGX101 hitchhikes along this internalization pathway to deliver its conjugated payload to the nuclear compartment of both activated endothelial cells and tumor cells in the tumor.

Figures

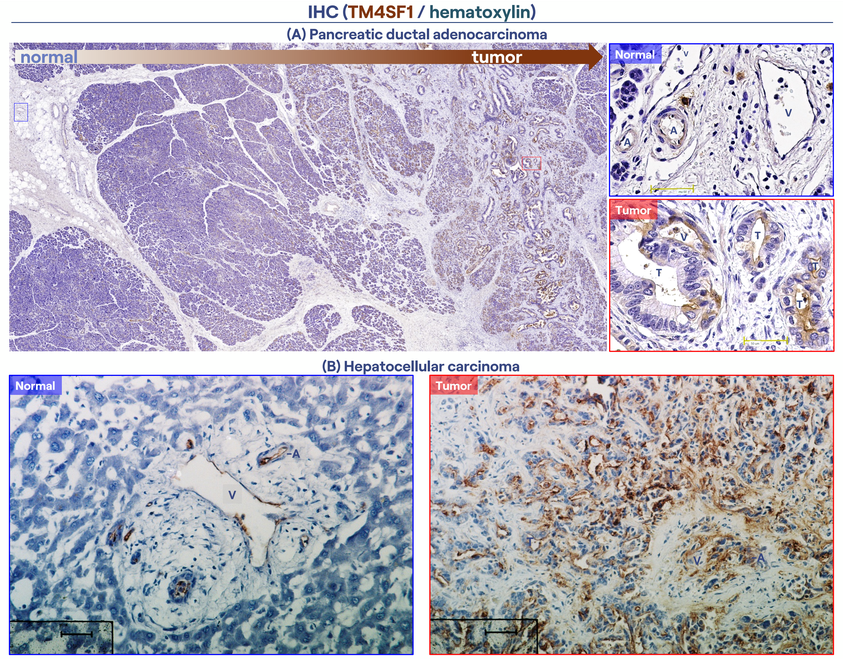


Figure 1. TM4SF1 is expressed at high levels in both cancer cells and tumor vascular endothelial cells. TM4SF1 immunohistochemical (IHC) staining was performed in **(A)** Pancreatic ductal adenocarcinoma and **(B)** Hepatocellular carcinoma. Representative images show that TM4SF1 is highly expressed in tumor blood vessels and tumor cells in both tumor types. TM4SF1 expression is much lower in adjacent normal tissues. **A**, artery; **V**, vein; T, tumor; Scales: 100 µm.

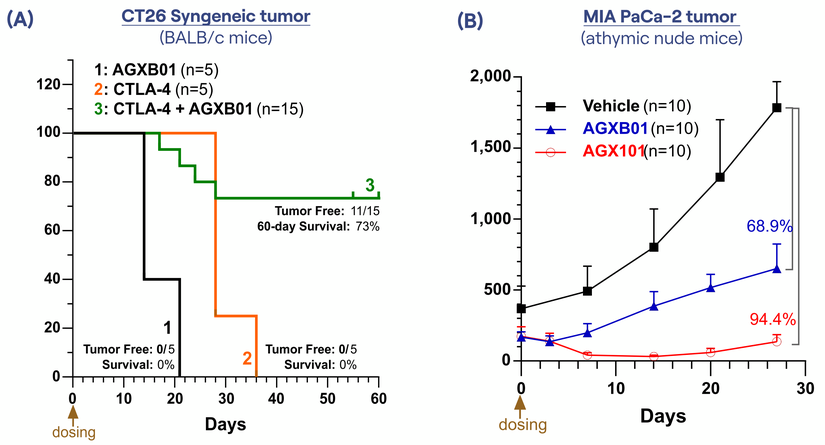


Figure 2. AGX101 demonstrates activity consistent with three mechanisms of action (MoAs). **(A)** AGXB01, a murine surrogate of AGX101 used in syngeneic models, was used to treat CT26 mouse colon cancer. A single 5 mg/kg dose of AGXB01 in combination with 3 mg/kg of an anti-mouse CTLA-4 antibody generated a 60-day tumor free survival rate of 73% versus 0% for the CTLA-4 or AGXB01 antibody alone (**MoA1,** Immune-activation through tumor wound). **(B)** AGX101 (target human tumor cell; **MoA3**) and AGXB01 (target mouse tumor vessels; **MoA2**) were independently used to treat human MIA PaCa-2 pancreatic cancer xenograft tumors. Both AGX101 and AGXB01 are efficacious at a single dose of 12 mg/kg.

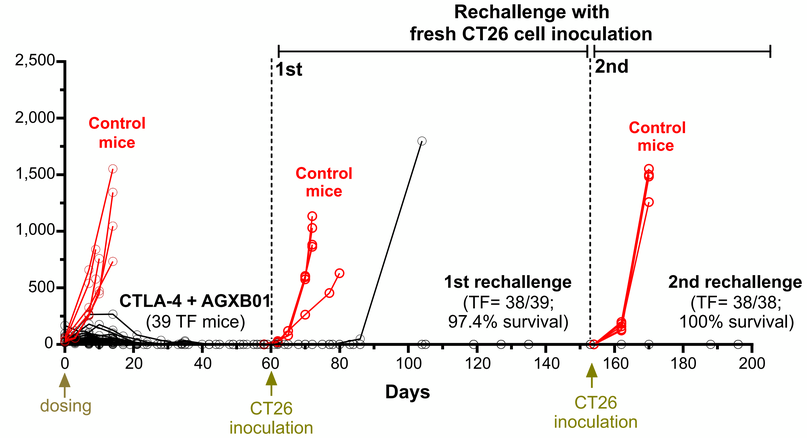


Figure 3. Rechallenge studies demonstrate durable anti-tumor immune memory against CT26 tumor cells. Of 39 mice that were tumor free following an initial treatment with the CTLA-4 (3 mg/kg) + AGXB01 (5 mg/kg) combo, thirty-eight (97.4%) remained tumor free in a 1st rechallenge inoculation 60 days following the original inoculation. All 38 remained tumor free in a 2nd rechallenge 72 days following the first rechallenge. The study demonstrates that the vast majority of mice developed adaptive anti-tumor immune memory against CT26 tumor cells.

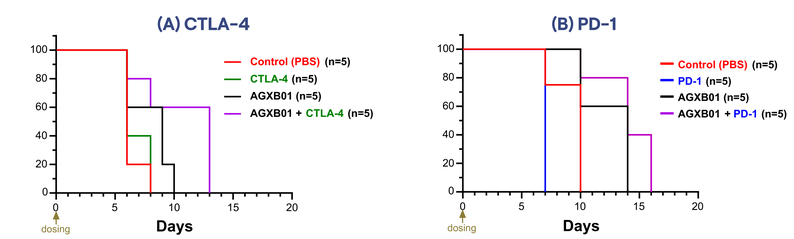


Figure 4. AGXB01 and checkpoint inhibitor combinations in B16F10 mouse melanoma. B16F10 mouse melanoma is an aggressive tumor that is non-responsive to **(A)** anti-CTLA-4 (2.5 mg/kg) and **(B)** anti-PD-1 (10 mg/kg) therapy. AGXB01 (20 mg/kg) combination with anti-CTLA-4 **(A)** or anti-PD-1 **(B)** antibodies enhanced survival time vs monotherapy of AGXB01 and vs anti-CTLA-4 antibody or anti-PD-1 antibody.