# SGN-B6A: A New MMAE ADC Targeting Integrin Beta-6 in Multiple Carcinoma Indications

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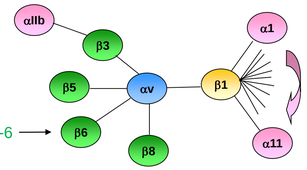
## Summary: SGN-B6A

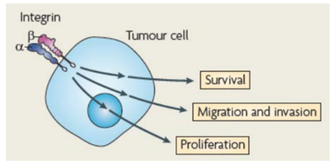

- SGN-B6A is a novel antibody-drug conjugate (ADC) targeting integrin beta-6
- Integrin beta-6 is expressed in a variety of solid tumors exclusively as a heterodimer with integrin alpha-v
- The antibody backbone is humanized 2A2, an antibody discovered at Seattle Genetics
  - h2A2 is specific for integrin beta-6, and does not bind to other integrin alph-v heterodimers
- SGN-B6A delivers the potent cytotoxin MMAE using the same vedotin technology that has been clinically validated with the FDA approved ADCs Adcetris®, Padcev®, and Polivy®
- The ADC rapidly internalizes upon binding to cells expressing integrin beta-6
- In multiple xenograft models, treatment with SGN-B6A resulted in tumor growth delay and regression in tumor volume
- SGN-B6A was tolerated in cynomolgus monkeys at 6 mg/kg q3w or 5 mg/kg weekly with dose-limiting hematologic toxicity typical of vedotin ADCs
- A phase I clinical study has recently been initiated to evaluate the safety and preliminary antitumor activity of SGN-B6A


## Integrin Beta-6 Background

- Member of the integrin family of adhesion protein isoforms that exist as alpha-beta heterodimers
  - Beta-6 forms exclusive heterodimers with alpha-v:




- Role in tissue remodeling & repair
  - Activates transforming growth factor-β
  - Regulates motility through extracellular matrix ligands
- Constitutively expressed at low levels in several epithelial tissues, upregulated in tissue repair response
- Tumors exploit remodeling function to promote invasiveness and metastasis
  - promotes epithelial to mesenchymal transition
  - promotes metastasis through inhibition of anoikis
- High expression is a poor prognostic indicator in multiple cancer types

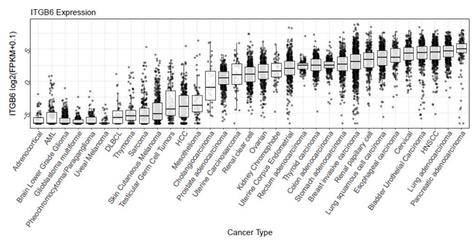



Nat. Rev. Cancer. 2010 Jan;10(1):9-22.

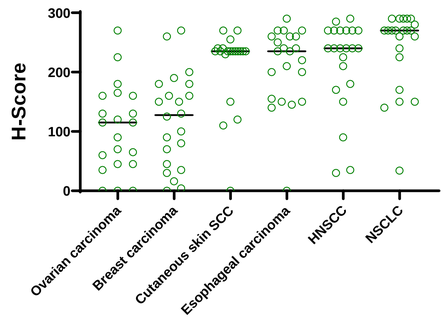
## Expression in Cancer

- Integrin beta-6 is well expressed in a variety of solid tumors

### RNASeq (The Cancer Genome Atlas)

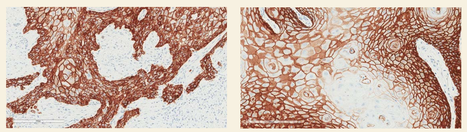



### Immunohistochemistry



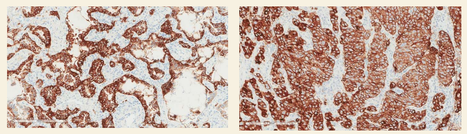

**Examples of strong IHC staining**

**Squamous Cell Carcinomas**



Head & Neck | Cutaneous Skin

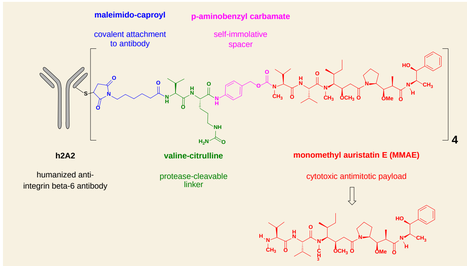
**Adenocarcinomas**



Non-Small Cell Lung | Ovarian

## SGN-B6A Composition

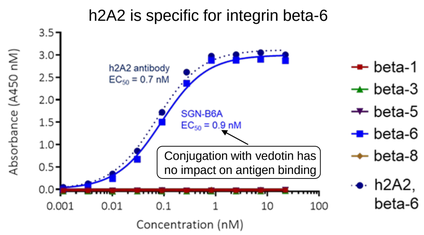
- The targeting component of SGN-B6A is the human anti-integrin beta-6 antibody h2A2, discovered and humanized at Seattle Genetics
- h2A2 uses the vedotin ADC technology to delivers the potent cytotoxin MMAE




## Binding and Internalization

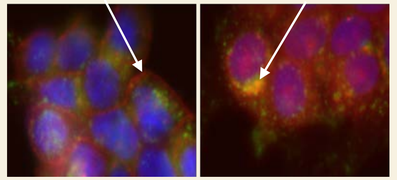
- h2A2 was selected for specific binding to integrin beta-6 and not other beta integrins that pair with alpha-v
  - Expected to confer greater tumor selectivity and reduced normal tissue target-mediated disposition than anti-alpha-v antibodies

h2A2 is specific for integrin beta-6




- Upon binding to cell-surface integrin beta-6, SGN-B6A rapidly internalizes and traffics through the endo-lysosomal pathway

**B6A staining on membranes** | **colocalization in lysosomes**

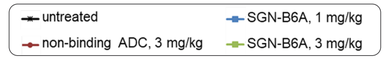


0 hr | 4 hr

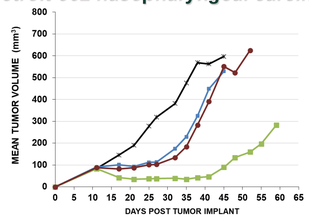
BxPC-3 cells treated with SGN-B6A were stained with an anti-human antibody to detect SGN-B6A (red), LAMP1 lysosome marker (green), and Hoescht to label nuclear DNA (blue). Images were collected at the indicated time points using the IN Cell Analyzer 2200 (GE Healthcare).

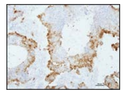
## Antitumor Activity

- SGN-B6A was evaluated in four carcinoma models with integrin beta-6 expression confirmed by IHC
  - ADC was dosed weekly for 3 doses at 1 and 3 mg/kg
  - SGN-B6A exhbited dose- and antigen-dependent growth delay and tumor volume reductions

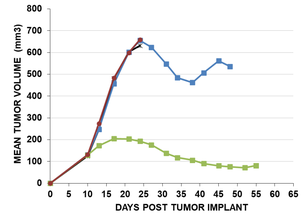


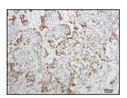

### Detroit-562 nasopharyngeal carcinoma model



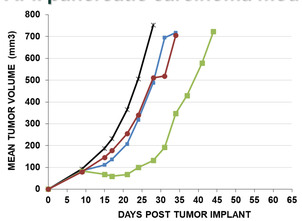



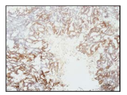
### SW780 bladder carcinoma model



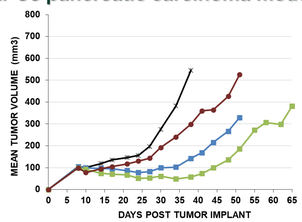



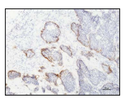
### HPAFII pancreatic carcinoma model



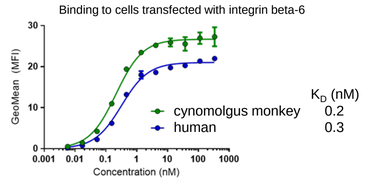
### BxPC3 pancreatic carcinoma model



## NHP Toxicology

- SGN-B6A is crossreactive with cynomolgus monkey integrin beta-6, validating this species as a toxicology model



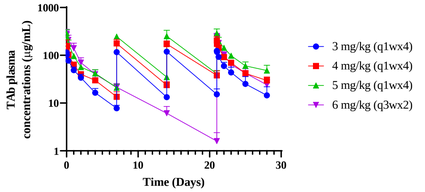

- The following dose groups were evaluated:

| Dosing Interval | Dose levels (mg/kg) | Number of doses |
|---|---|---|
| weekly | 3, 4, 5 | 4 |
| every 3 weeks | 6 | 2 |

- SGN-B6A was tolerated in all dose groups
- Dose-limiting hematologic effects observed
  - Decreased white blood cells, neutrophils, and reticulocytes
- Profile similar to other vedotin ADCs

### NHP Pharmacokinetics

- SGN-B6A exhibited approximately dose-proportional exposure
- Terminal $t_{1/2}$ approximately 3 days




| SGN-B6A Dose (mg/kg) | $C_{max}$ (ng/mL) | $AUC_{(0-7d)}$ (day*ng/mL) | $t_{1/2}$ (day) | CL (mL/day/kg) | $V_{ss}$ (mL/kg) |
|---|---|---|---|---|---|
| **3** | 115000 | 199000 | 2.31 | 13.6 | 40.4 |
| **4** | 162000 | 282000 | 2.58 | 12.4 | 42 |
| **5** | 299000 | 426000 | 2.98 | 9.86 | 35.9 |
| **6** | 295000 | 501000 | 3.53 | 9.77 | 37.6 |

Parameters determined by non-compartmental analysis with Phoenix WinNonlin (Certara)

## Conclusions

- Integrin beta-6 is a promising ADC target owing to its broad expression in carcinomas and rapid internalization when bound by antibody
- SGN-B6A is a novel vedotin ADC with a compelling preclinical profile and potential activity in a variety of solid tumor indications
- Activity and tolerability similar to approved vedotin ADCs
- A Phase I trial to evaluate SGN-B6A is now recruiting patients (NCT04389632)

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