



# Preclinical evaluation of SAR566658 (huDS6-DM4) in mice bearing human tumor xenografts of breast, ovarian, lung, cervical and pancreatic cancer



Christina Carrigan, Claudia Zuany-Amorim, Michele F. Mayo, Daniel J. Tavarez, Robert J. Lutz, Anne E. Kellogg, Veronique Blanc, Patricia Vrignaud, Marie-Christine Bissery, and Gillian Payne. ImmunoGen, Inc, Waltham, MA, sanofi-aventis, Vitry-sur-Seine, France, East Carolina University Brody School of Medicine, Greenville, NC

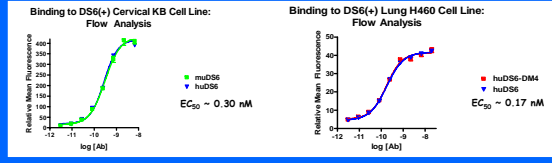
Acknowledgements: Waiyong Sun, Hongsheng Xia; Lisa Garrett; Thierry Harcourt

## Abstract

SAR566658 (huDS6-DM4) consists of the humanized monoclonal antibody, huDS6, with DM4, a potent cytotoxic maytansinoid, attached, and targets solid tumors such as ovarian, breast, cervical, lung and pancreatic carcinomas. The DS6 antibody was raised in mice using human serous ovarian cancer ascites as the immunogen and recognizes an O-linked tumor-associated sialoglycoprotein on Muc1. The DS6 antibody was humanized using resurfacing technology that preserved the binding affinity (0.3 nM) of the antibody and the cytotoxic activity (1 nM) and selectivity of the conjugate for antigen-positive tumor cells.

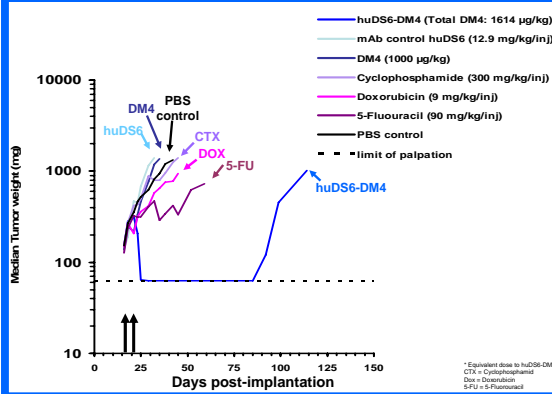
SAR566658 is active in a dose-dependent manner against several human xenograft solid tumors in immunodeficient mice. For example, mice bearing tumors (142 mg) of the human breast tumor cell line, UI50 BCA-1, a tumor model refractory to standard chemotherapeutic agents, were treated twice per day on days 17 and 21 with IV doses of SAR566658. At the highest non-toxic dose (HNTD) of 20.8 mg/kg/injection (total dose: 83.2 mg/kg), SAR566658 induced a body weight loss of 11.4% and was considered highly active with 100% complete tumor regressions (CR), a 5.2 log cell kill (lck = tumor growth delay/3.32 x tumor doubling time) and 40% of the mice tumor free at the end of study (day 141). Lower doses (51.6 and 32 mg/kg total dose) were also highly active, causing 100% and 80% CR with a 5.3 and 3.3 lck, respectively. The lowest active dose was 19.6 mg/kg total dose (1.9 lck). On the other hand, treatment with either the huDS6 antibody (total dose: 51.6 mg/kg) or free DM4 (1 mg/kg; equivalent DM4 dose to 51.6 mg/kg SAR566658) showed no anti-tumor activity. In addition, standard chemotherapeutics doxorubicin and cyclophosphamide (highest dose tested 9.0 mg/kg/injection and 300 mg/kg/injection, respectively) were inactive against the UI50 BCA-1 xenografts, while 5-fluorouracil showed modest activity (2.0 lck) at its HNTD (90 mg/kg/injection). Dose-dependent activity with SAR566658 was also observed in other antigen-positive human xenografts with 100% CR achieved in breast (MX-1 at 26.8-69.6 mg/kg), cervical (WISH at 3.9-46 mg/kg), ovarian (OVCAR5 at 16-46 mg/kg), pancreatic (Capan-2 at 5.2-23 mg/kg) and lung (NCI-H460 at 43.4 mg/kg) models. The dependence of SAR566658 activity on binding to target antigen was demonstrated in the human ovarian OVCAR5 model where the anti-tumor activity of SAR566658 was inhibited by pretreatment (2 hours earlier) of mice with excess huDS6 antibody. SAR566658 was not only able to elicit CR and tumor-free survivors in mice with advanced tumors (100-200 mg at the start of treatment), but also in mice with bulky tumors (~500 mg) arising from recurrent disease. The robust activity of SAR566658 in preclinical models provides a strong rationale for its clinical development.

## HuDS6-DM4 retains binding affinity with respect to murine DS6



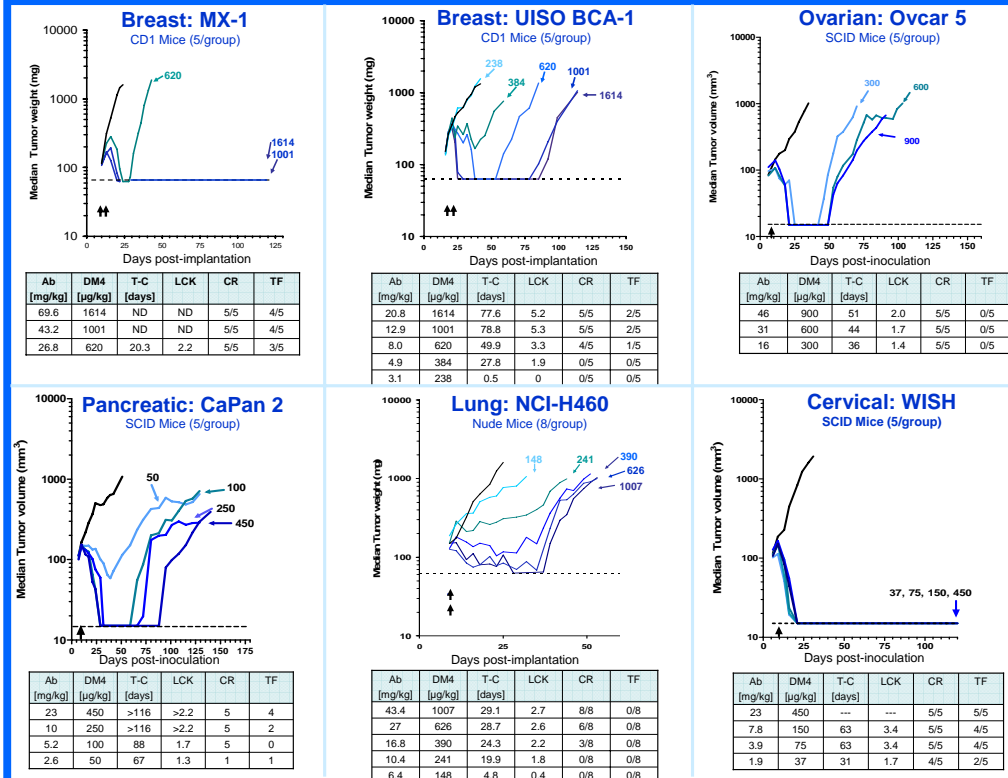
## HuDS6-DM4 is highly active against refractory breast model UI50 BCA-1

Nude mice were treated twice per day on days 17 and 21 with huDS6-DM4 and standard treatment doses were given for reference compounds. All doses are the highest non-toxic dose (HNTD)

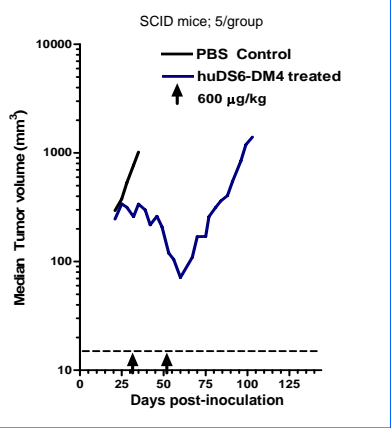


## HuDS6-DM4 exhibits dose-dependent activity against a number of disease indications

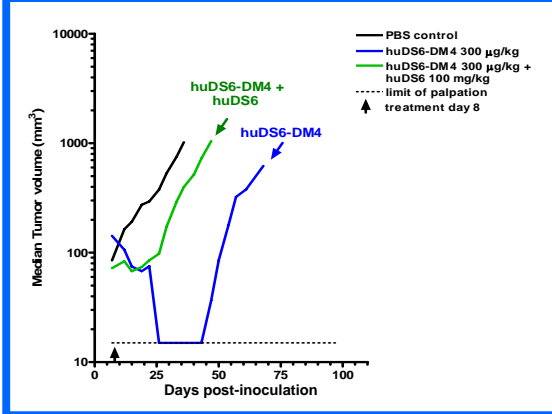
Subcutaneous DS6-positive human tumor xenografts were treated with huDS6-DM4 as an IV injection (dosed by DM4 [µg/kg]); The size of the median tumor on day assessed is plotted.



## HuDS6-DM4 is active in bulky tumors Ovar 5 xenograft model

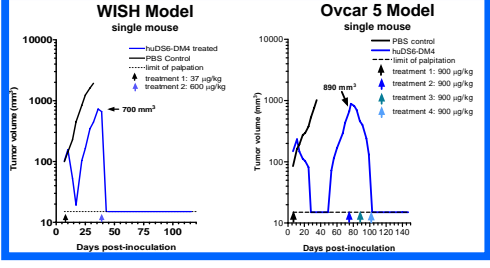


## HuDS6-DM4 shows specific targeting in an Ovar 5 xenograft model huDS6-DM4 shows diminished efficacy in the presence of naked huDS6



LCK = log cell kill CR = complete response TF = tumor free --- Limit of palpitation - - - PBS control ↑ treatment

## Complete regression of large recurrent tumors can be achieved with huDS6-DM4



## Conclusions

- HuDS6-DM4 is active against several solid human xenograft tumors including a refractory model
  - shows dose-dependent activity
  - indications include breast, cervical, lung, ovarian and pancreatic cancers
- HuDS6-DM4 is effective for treatment of large tumors
  - Tumors ranging from 175-516 mm<sup>3</sup> responded to huDS6-DM4
- Complete responses are achieved when larger recurrent tumors (> 500 mm<sup>3</sup>) are retreated with huDS6-DM4
- HuDS6-DM4 shows antigen-dependent tumor targeting

The HuDS6-DM4 in vivo activity strongly supports its advancement to clinical testing