Novel albumin-binding maytansinoids inducing long-term partial and complete tumor regressions in several human cancer xenograft models in nude mice


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INTRODUCTION & RATIONALE

Maytansine and its analogs (e.g. DM1 and DM4) are potent microtubule-targeting compounds with a narrow therapeutic window. So far, only T-DM1, an antibody-maytansinoid conjugate targeting the HER2 receptor, has been approved for the treatment of HER2+ resistant breast cancer.

Our design of two novel albumin-binding maytansinoids (LADR-9 and LADR-10) is based on:
- Identification of two novel maytansine-based highly potent payload (ANSA-05, ANSA-13), selected from screening a library of maytansinoids in vitro (Poster #1657).
- Derivationization with a new water-solubilizing linker (SULF-07) resulting in LADR-9 and LADR-10 which bind in situ to the Cys-34 position of endogenous albumin.
- Accumulation of the drug-albumin conjugate in tumor tissue
- Acid-mediated drug release at the tumor site

IN VITRO EVALUATION

pH-Dependent stability of both drug-albumin conjugates

The serum albumin (SA) conjugates of LADR-9 and LADR-10 are cleared under acidic conditions and release the active component.

Plasma stability of both free drugs and drug-albumin conjugates

Both albumin-binding maytansinoids LADR-9 and LADR-10 were evaluated in six human tumor xenograft models and showed excellent antitumor activity inducing long-term partial and complete remission in all rodent models. In addition, both albumin-binding drugs were consistently superior over maytansine which was essentially inactive (statistically significant results). Importantly, even the treatment of large tumors with starting volumes up to 350 mm³ was highly effective.

In a few cases (namely, LXFE 937, MDA-MB 468 and HN 10913), which depended on the tumor type, significant body weight loss (>20%) with maytansine as well as with the albumin-binding drugs was observed in the animals.