PRECLINICAL EVALUATION OF PEGYLATED LIPOSOMAL DOXORUBICIN OR DOXORUBICIN WITH MATRC-101 IN THE EMT6 SYNGENEIC MOUSE MODEL

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Background We previously described ATRC-101, a fully human, engineered IgG1 antibody which is currently under evaluation in the clinic as a monotherapy for solid tumors. A chimeric version of this antibody expressed on a mouse IgG2a (mATRC-101) has shown robust anti-tumor activity as a monotherapy in the EMT6 syngeneic tumor model. In order to assess the potential utility of ATRC-101 in combination with chemotherapeutic agents, non-clinical studies were performed to assess the efficacy of mATRC-101 in combination with chemotherapeutic agents, including Doxorubicin and pegylated liposomal Doxorubicin (PLD), and the impact of these anti-tumor small molecules on mATRC-101 immunoreactivity in mouse tumor and normal tissues.

Methods Female BALB/c mice with established EMT6 tumors were dosed with mATRC-101 (1 or 3 mg/kg) or vehicle intraperitoneally (IP) twice weekly plus Doxorubicin (2 or 5 mg/Kg) or vehicle (saline) IV once weekly following randomization on Day 6. Statistical analyses of tumor volumes were performed using the normalized area above the curve and the normalized growth rate metrics developed at Atreca. One-sided log-rank (Mantel-Cox) test was used to assess survival advantage relative to the indicated reference group. P-values ≤ 0.05 were considered significant. In monotherapy studies with Doxorubicin and PLD, EMT6 tumor and non-tumor bearing mice were dosed with vehicle or Doxorubicin (2, 10 mg/kg) or PLD (1, 2, 5, 10 mg/kg). Normal mouse tissues were collected at 24 hours and 2 weeks after the last dose. Reactivity for mATRC-101 in EMT6 tumor and normal mouse tissues was evaluated by immunohistochemistry

Results The combination of 3 mg/kg mATRC-101 and 5 mg/kg Doxorubicin demonstrated significant tumor growth inhibition compared to either monotherapy, or vehicle ($p < 0.05$) through Day 22. Moreover, the combination resulted in a significant survival benefit compared to vehicle and 5 mg/kg Doxorubicin monotherapy ($p < 0.0005$). Immunohistochemical analyses of mATRC-101 reactivity in EMT6 tumors from mice treated with chemotherapy alone showed apparent dose-dependent increase in immunofluorescence intensity with increasing concentrations of Doxorubicin or PLD. Furthermore, tissue cross-reactivity studies in selected normal organs from mice treated with Doxorubicin or PLD demonstrated no reactivity above vehicle.

Conclusions This study provides non-clinical evidence that administration of mATRC-101 in combination with Doxorubicin increases anti-tumor activity in the EMT6 model. Exposure to Doxorubicin or PLD in EMT6 tumor-bearing mice increased mATRC-101 immunoreactivity in the tumor, in a dose-dependent manner. Moreover, mATRC-101 immunoreactivity in normal tissues was not influenced by Doxorubicin or PLD. Taken together, these findings support clinical evaluation of the combination of ATRC-101 and doxorubicin.

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