MORAb-202: a Folate Receptor-α (FRA)-targeting antibody-drug conjugate, exhibiting targeted antitumor activity and bystander elimination of cancer-associated fibroblasts

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Abstract

Triple negative breast cancer (TNBC) is a highly metastatic disease with very poor long-term prognosis. Because of the lack of well-defined molecular targets, traditional chemotherapy is the only therapeutic regimen for TNBC. Among the available options, eribulin has been approved by Phase II study 320 for patients with metastatic breast cancer (BCa) who have previously received at least two chemotherapeutic regimens for metastatic disease, including an anthracycline and a taxane in either the adjuvant or metastatic setting. Another Phase III study 301 showed eribulin was not shown to be superior to standard of care with respect to OS or PFS. However, subpopulation analysis from both 301 and 305 found that survival benefit achieved by eribulin was observed in HER2-negative and triple negative breast cancer (TNBC).

Folate Receptor alpha (FRA) is a GPI-anchored membrane glycoprotein which has limited expression in normal tissue, but is highly overexpressed on a large number of cancers of epithelial origin including non-small cell lung cancer (NSCLC), ovarian cancer and TNBC. These features make FRA an attractive target for the treatment of BCa using targeted therapeutic approaches.

Ferlatuzumab, a humanized monoclonal antibody targeting FRA, has been investigated in multiple clinical trials enrolling patients over-expressing FRA. MORAb-202, a novel antibody-drug conjugate (ADC), consisting of ferlatuzumab conjugated to eribulin, targets FRA over-expressed by a variety of tumor types including TNBC. Upon binding and internalization, it is hypothesized that the ferlatuzumab moiety would exert a direct effect on FRA-positive tumor cells and a bystander effect on FRA-negative tumor cells and, importantly, tumor-associated stromal cells within the tumor microenvironment.

To address this hypothesis, we evaluated the in vivo efficacy of MORAb-202 against a FRA-positive TNBC patient derived xenograft (PDX) model. Single-agent administration of eribulin and MORAb-202 mediated statistical tumor regression compared to vehicle control (P<0.001). Additionally, one animal treated with MORAb-202 showed complete and durable tumor regression. In order to examine the effects of MORAb-202 treatment on the tumor microenvironment, we harvested tumors both prior to treatment and five days post-treatment. Immunofluorescent staining was used to assess the target specific engagement of MORAb-202 to FRA-positive regions of the tumors.

Strong membrane staining of MORAb-202 was observed, while no staining was seen in the adjacent stromal regions. MORAb-202 also had demonstrable effects on the tumor microenvironment via reduction of the number of FRA-negative cancer-associated fibroblasts (CAF) present. To further evaluate whether these effects on CAF are part of MORAb-202 mode of action (MOA), we tested the anti-tumor efficacy and effects on the tumor microenvironment in a surrogate FRA-positive in vivo model. Tumors were isolated on days 3, 5, 7, and 9 post-treatment. The reduction in CAF visualized by alpha-smooth muscle actin staining, was directly proportional to overall tumor reduction.

In both studies, single dose MORAb-202 showed dramatically greater efficacy than more equivalent dosing of eribulin alone in vivo PDX and xenograft models. Histological analyses revealed unique modes of action of MORAb-202 over antibody or paclitaxel alone. These results suggest a potential benefit of MORAb-202 in the treatment of TNBC.

Summary

1. In vivo anti-tumor efficacy of MORAb-202 was observed in human xenograft models and both NSCLC and TNBC PDX models including a model with low FRA expression.
2. MORAb-202 specifically targeted FRA+ tumor cells in the TNBC PDX model, shown by anti-ferlatuzumab and anti-erbulin IF staining.
3. The network of cancer associated fibroblasts in the tumor microenvironment was affected by MORAb-202 treatment. Diminishment of overall CAF numbers combined with more structural re-organization was present in samples treated with MORAb-202.

These data warrant further investigation of MORAb-202 in clinical trials.

References

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Figure 1: Structure of MORAb-202

Figure 2: MORAb-202 Mechanism of Action

Figure 3: In vivo efficacy of MORAb-202 on NSCLC PDX model

Figure 4: Anti-tumor efficacy of MORAb-202 in a FRA-low TNBC PDX model

Figure 5: Target Engagement of MORAb-202 on TNBC PDX Tumors

Figure 6: Direct cytotoxicity of MORAb-202 on FRA positive NCI-H2110 xenograft tumor

Figure 7: MORAb-202 effect on cancer associated fibroblasts in TNBC PDX tumors

Figure 8: MORAb-202 effect on cancer associated fibroblasts in TNBC PDX tumors

Figure 9: Time course showing the reduction of CAF in NCI-H2110 model caused by MORAb-202

In vivo anti-tumor efficacy of MORAb-202 was evaluated in a FRA-positive, non-small cell lung carcinoma PDX model on athymic mice. Mice were administrated single intravenous administration of either ferlatuzumab, eribulin, 202, Antibody-drug conjugate ferlatuzumab, or vehicle only at day 0 (Vehicle). At the end of the study, all tumors were collected for IHC. (A) Tumor growth: both ADCs and MORAb-202 produced complete regression (R0) in 6/6 animals. (B) Ferlatuzumab was positive in the xenograft only at day 75. (C) IHC expression on re-grown tumors on Day 75 showed decreased differences.


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