MORAB-202 A FOLATE RECEPTOR ALPHA-TARGETED ANTIBODY-DRUG CONJUGATE SHOWS A HIGHLY POTENT ACTIVITY AGAINST A PANEL OF FRA-EXPRESSING TUMORS


INTRODUCTION

A new biomarker of recent interest in the cancer field is folate receptor alpha (FRA), a membrane-bound protein with high affinity for binding and transporting folic acid into cells. Overexpression of FRA may confer a growth advantage to tumors by increasing folate uptake and effect cell proliferation via alternative cell signaling pathways (1). FRA levels have been found to be elevated in tumors of epithelial origin compared to normal tissue, including triple-negative breast cancer (TNBC) (2). Due to an absence of potent targeted therapy for this breast cancer subtype, the finding that a significant number of TNBCs express abundantly FRA suggests an important population of patients may benefit from FRA-targeting therapy.

Eighty-five percent of preclinical agents entering oncology clinical trials fail to demonstrate sufficient safety or efficacy to gain regulatory approval (3). This failure rate shows a weak understanding of the complexity of human cancer, the continued limitations of the predictive value of existing preclinical models and the scale at which cancer models are investigated in the preclinical setting (4). There is a need for new experimental models that better replicate the diversity of human tumor biology in a preclinical setting. It is now evidenced that patient-derived xenografts (PDx) recapitulate human tumor biology and help predict patient drug response (5) by directly comparing drug responses in patients and their corresponding xenografts. To extend such observations to a greater number of human cancers, we have generated in collaboration with Eisai an extensive collection of breast PDXs.

The national IMODI (Innovative MODels Initiative) consortium collection

• Highly efficacious in tumor cell xenograft models
• Serum-stable
• Bystander effect in mixed tumor cell populations
• Off-target killing

With eribulin without targeting vector.

Preclinical Antitumor Efficacy

In IM-BRE-563, a higher response was observed with MORAb-202-eribulin than eribulin alone, suggesting that preclinical antibody-drug conjugates against FRA should be tested in clinical trials.

Conclusions and perspectives

> FRA expression could be used for MORAB-202 activity biomarker.

> Preclinical antitumor activity of MORAB-202 is dependent on FRA expression.

> At equivalent dose MORAB-202 showed a higher antitumor activity when compared to free eribulin in preclinical studies. In high expression FRA tumor, to observe similar antitumor activity in preclinical studies, the dose of eribulin without vectorization would require to be enhanced by 32-fold compared to targeted eribulin. At this dose of eribulin, a body weight loss is observed and a tumor relapse occurred in all treated animals, whereas no relapse was observed for mice treated with MORAB-202.

> TNBC that does not express estragen, progestrone or the HER2 receptor are refractory to available targeted therapies for breast cancer treatment, such as HER2-directed therapy (trastuzumab, T-DM1) and endocrine therapies (tamoxifen or letrozole) should be sensitive to MORAB-202 treatment in FRA-expressing tumors.

References