Therefore, improved therapies targeting these TAAs are needed for unmet medical needs. ADCs have shown encouraging early clinical efficacy in multiple tumors recently (for example, see ref 1). However, majority of patients still did not respond. Despite MUC1 being a well-known tumor associated antigen (TAA), earlier anti-MUC1 agents have shown limited efficacy in the clinic [2-4]. Notably, one gets HER3xMUC1, demonstrated enhanced in vitro internalization activity and superior in vivo anti-tumor activities in a number of HER3 and MUC1 double positive PDX models. DM002-BLD1102 further demonstrated strongly cross-reactive with human and cynomolgus monkey antigens with higher capacity and internalized with higher rates than its parental mAb. DM002-vcMMAE, both of these conjugates tested to novel DNA topoisomerase I inhibitor-linker-payload conjugates (BLD1102) potentiated growth of HER3 and MUC1 double positive PDX tumors. The DM002 bsADCs also showed more potent in vivo efficacy than its parental anti-HER3 ADCs, consistent with their in vitro internalization activities. DM002-BLD1102 further demonstrated strongly anti-tumor activity in DM002-vcMMAE-resistant PDX models, suggesting the superiority of this new DNA topoisomerase I inhibitor-payload conjugate over the classical MMAE conjugated to DM002. DM002 bsAbs, in particular DM002-BLD1102, which targets HER3xMUC1, demonstrated enhanced in vitro internalization activity and superior in vivo anti-tumor activity in a number of HER3 and MUC1 double positive PDX models, raising their promising potential candidates for treating HER3 and MUC1 positive tumors.

DM002 bsAbs demonstrated increased cell binding avidity

A

(A) Analysis of data in the cancer genome atlas (TCGA) database revealed co-expression of HER3 and MUC1 in multiple solid tumors (left panel). In the lung adenocarcinoma (left), breast invasive carcinoma (middle) and pancreatic adenocarcinoma (right panel), HER3 and MUC1 were co-expressed in over 20% of the patients, especially in LUSM (lung squamous cell carcinoma), BRCA (breast invasive carcinoma), and PDAC (pancreatic adenocarcinoma). (B) Analysis of data in multiple cancer cell lines revealed a number of HER3 and MUC1 double positive PDX models.

B

Superior anti-tumor activity of DM002 A-BLD1102 in benchmark ADC-resistant BP0226 and BP0170 PDX models

DM002 A-BLD1102 exhibited superior anti-tumor efficacy over the conjugates to tGGFG-Dxd and vcMMAE

A

(D) DM002 A/B-vcMMAE also showed enhanced anti-tumor activity versus parent monoclonal antibody (mAb) ADCs.

B

DM002 A/B-vcMMAE demonstrated robust anti-tumor activity in two CDX models

C

DM002 bAbs exhibited potent anti-tumor activity in PDX models

DM002 bAbs showed enhanced internalization in NUGC4 tumor cells

PRECLINICAL EVALUATION OF FULLY HUMAN BISPECIFIC ANTIBODY-DRUG CANDIDATES TARGETING HER3 AND THE JUXTAMEMBRANE REGION OF MUC1

INTRODUCTION

HER3 and MUC1 are co-expressed in multiple solid tumors.

DM002 bsAbs showed enhanced internalization in NUGC4 tumor cells

DM002 bsAbs demonstrated increased cell binding avidity

DM002 A-B-vcMMAE demonstrated robust anti-tumor activity in two CDX models

DM002 A/B-vcMMAE exhibited potent anti-tumor activity in HER3-low PDX models

SUMMARY

REFERENCES