MBRC-101: a novel antibody-drug conjugate (ADC) targeting the membrane-associated tyrosine kinase receptor EphA5

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Introduction

MBRC-101 is a potent ADC for the treatment of EphA5-expressing solid tumors

• EphA5 is a member of the receptor tyrosine kinase family of proteins with functional roles in axonal guidance during embryonic development[1,2,3]

• EphA5 expression has been reported in lung, gastric, ovarian and pancreatic cancers, with restricted expression in normal tissues[4,5,6]

• Differential expression in cancers and accessibility through the systemic circulation support the development of antibody-based therapies against EphA5[7,8]

EphA5 is expressed in solid tumors

• Archival cancer tissue sections of various indications were evaluated by immunohistochemistry (IHC)

• EphA5 membrane expression was detected in 78% (18/23) of triple negative and 88%(23/26) of hormone receptor-positive breast cancer tissue samples

• EphA5 membrane expression was also detected in 85% (29/34) of lung squamous cell carcinoma, 73% (16/22) of lung adenocarcinoma, 70% (7/10) of gastric, 70% (15/22) of colorectal, and 50% (6/12) of pancreatic patient tumors tested

• EphA5 expression was not detected in adjacent, non-malignant normal tissue

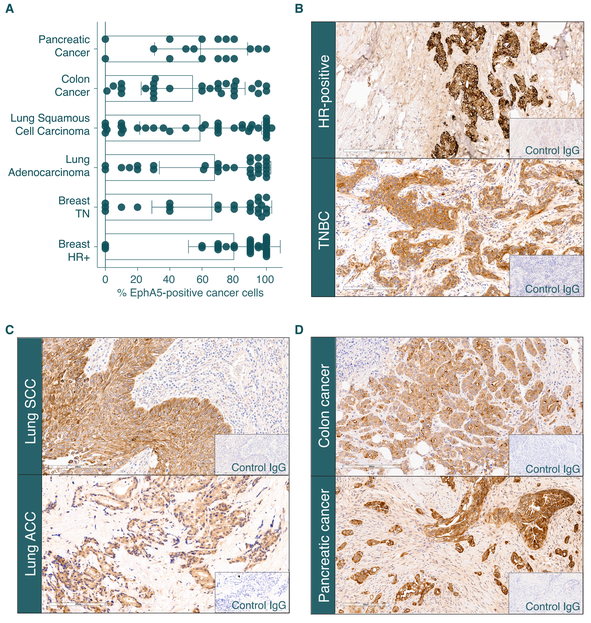

Figure 1. Expression of EphA5 across multiple cancer types. (**A**) Percentage of EphA5-expressing cells in solid tumors. Testing for EphA5 expression by IHC used a commercial rabbit polyclonal antibody. IHC staining was performed on the Leica BOND III automated platform and analyzed by expert pathologists. (**B**-**D**) Representative images showing EphA5 expression in (**B**) breast cancer, (**C**) lung cancer and (**D**) pancreatic and colorectal cancers.

Methods and Results

MBRC-101

• MBRC-101 is composed of a humanized anti-EphA5 IgG1 antibody conjugated to MMAE

• The anti-EphA5 antibody binds to EphA5 specifically and with high affinity (KD = 2.05 x 10^{-9} M)

• The anti-EphA5 antibody/EphA5 complex internalizes rapidly in EphA5-expressing cells

• MBRC-101 is cytotoxic to EphA5-expressing cells in a concentration-dependent manner

Antibody internalization

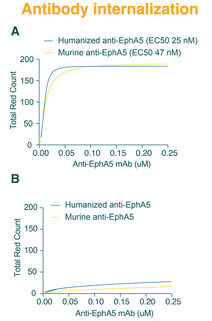

Figure 2. (**A**) Antibody internalization was visualized and quantified using the Incucyte® real-time live cell imaging analysis. (**B**) Antibody internalization was not detected in EphA5-negative cells.

MBRC-101 cytotoxicity

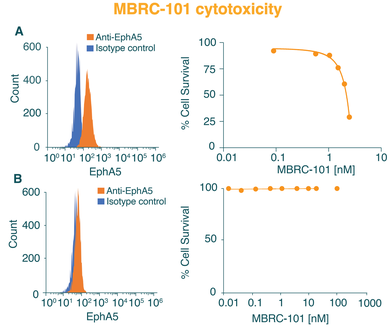

Figure 3. (**A**) Flow cytometry analysis confirming EphA5 expression on cells. MBRC-101 kills EphA5-positive cells in a dose dependent manner. (**B**) Flow cytometry analysis confirming absence of EphA5 on control cells. MBRC-101 does not affect viability of control cells.

MBRC-101 is highly potent *in vivo*

• Weekly administrations of intravenous (IV) MBRC-101 showed dose-dependent, robust, and reproducible anti-tumor activity in patient-derived xenograft models

• Partial tumor responses were observed at doses of 2.5 mg/Kg IV and complete tumor responses at 5 mg/Kg IV

• Doses up to 20 mg/Kg IV were well-tolerated with no observable weight loss

Anti-tumor activity in PDX models of TNBC

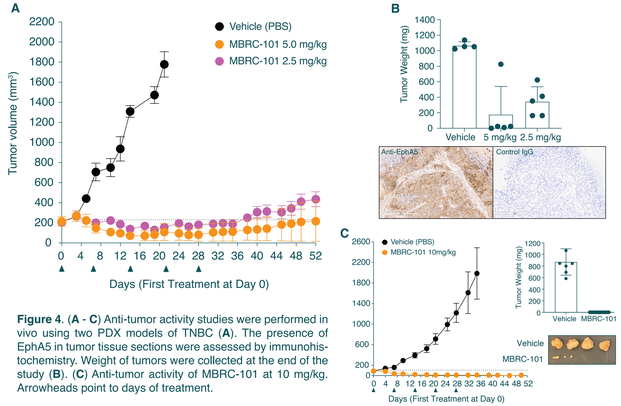

Figure 4. (**A - C**) Anti-tumor activity studies were performed in vivo using two PDX models of TNBC (**A**). The presence of EphA5 in tumor tissue sections were assessed by immunohistochemistry. Weight of tumors were collected at the end of the study (**B**). (**C**) Anti-tumor activity of MBRC-101 at 10 mg/kg. Arrowheads point to days of treatment.

Anti-tumor activity in PDX model of H&N SCC

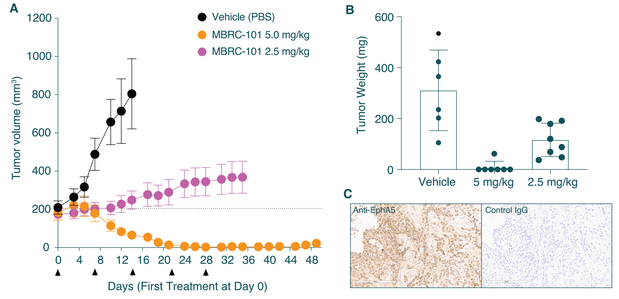

Figure 5. (**A - C**) Anti-tumor activity studies were performed in vivo using a PDX model of H&N sqamous cell carcinoma (**A**). Weight of tumors were collected at the end of the study (**B**). The presence of EphA5 in tumor tissue sections were assessed by immunohistochemistry (**C**).

Anti-tumor activity in PDX model of lung SCC

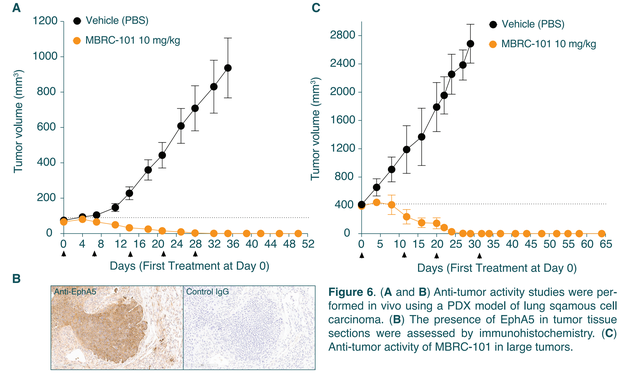

Figure 6. (**A** and **B**) Anti-tumor activity studies were performed in vivo using a PDX model of lung sqamous cell carcinoma. (**B**) The presence of EphA5 in tumor tissue sections were assessed by immunohistochemistry. (**C**) Anti-tumor activity of MBRC-101 in large tumors.

Toxicokinetics of MBRC-101 in rats and NHP

• Half-life of MBRC-101 in cynomolgus monkeys = 7 to 11 days

• Half-life of MBRC-101 in rats = 8 to 20 days

• Highly stable linker leads to equivalent levels of total ADC and total antibody with very low levels of free MMAE (< 0.01 %)

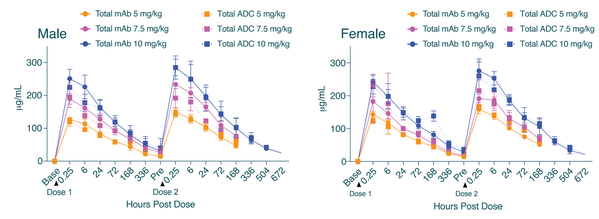

Figure 7. Due to the stability of MBRC-101, exposure for total ADC and total antibody were highly concordant. Both sexes demonstrated similar pharmacokinetics with no accumulation in the second dose; Cmax at 0.25 hours was consistent with IV bolus.

Toxicology findings attributed to payload and not target-related

Toxicology study design for MBRC-101

Species	Cynomolgus Monkey		Sprague-Dawley Rat	
Study	DRF	GLP	DRF	GLP
Dosing	2 IV boluses	2 IV boluses	2 IV boluses	2 IV boluses
Interval	3 wk	3 wk/4 wk recovery	3 wk	3 wk/4 wk recovery
Dose (mg/kg)	0, 5, 10, 15	0, 5, 7.5, 10	0, 5, 10, 20, 30	0, 10, 20, 30
HED* (mg/kg)	1.67, 3.2, 5	1.67, 2.5, 3.2	1, 2, 3, 5	2, 3, 5
#/Group/Sex	1F/2M or 1M/2F	3 + 2 recovery	5	10 + 5 recovery

Cynomolgus monkey - toxicology findings

Dose (mg/kg)	HED* (mg/kg)	Finding	Recovery
15	5	**Morbidity:** (n=1) due to sepsis	No
10 - 15	3.2 - 5	**Testicle:** bilateral degeneration/decreased sperm **Ovary:** decreased secondary and tertiary follicles **Neutrophils:** decreased	No No Yes
5 - 15	1.67 - 5	**Lymphocytes:** decreased in blood and spleen **Red blood cell mass:** decreased	Yes Yes
10	3.2	**Cornea:** minimal bilateral degeneration at the limbus	Yes

Sprague-Dawley rat - toxicology findings

Dose (mg/kg)	HED* (mg/kg)	Finding	Recovery
20 - 30	3 - 5	**Liver** • Hepatocellular necrosis, increased ALT, AST • Altered function: increased total bilirubin, ALP, cholesterol and triglycerides (30 mg/kg only)	Yes Yes
		Neutrophils: decreased	Yes
		Red blood cell mass: decreased	Yes
		Cornea: increased mitotic figures and apoptosis	Yes
10 - 30	2 - 5	**Lung:** increased alveolar macrophage and aveolar hyperplasia	No
		Testicle: bilateral degeneration with decreased sperm	No
		Lymphocytes: decreased in blood and thymus	Yes

*Human equivalent dose

MBRC-101-001 Phase 1/1b Trial

• A Phase 1/1b trial of MBRC-101 in patients with advanced metastatic solid tumors refractory to standard treatment activated on November 7, 2023 (NCT06014658)

• As of March 20, 2024, 12 patients had received MBRC-101 in Phase 1 dose escalation with no dose limiting toxicities (DLTs) observed

Conclusions

• Extensive in vitro testing showed that MBRC-101 binds to EphA5 exclusively, it is rapidly internalized and is cytotoxic to cells expressing EphA5

• MBRC-101 is highly potent against PDX models of TNBC, adenocarcinoma and squamous cell carcinoma of the lung, and head and neck squamous cell carcinoma

• MBRC-101 was well tolerated at doses up to 30 mg/kg in rats and 10 mg/kg in monkeys. Toxicologic findings in both species were attributed to the MMAE payload and not target-related

• Highest non-severely toxic dose (HNSTD) in monkeys was 10 mg/kg (HED = 3.2 mg/kg). In alignment with ICH S9, 1/6 of the monkey HNSTD was used to determine the human start dose of 0.5 mg/kg

• A Phase 1/1b trial of MBRC-101 is open and currently enrolling patients (NCT06014658)

References

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