ANTITUMOUR ACTIVITY OF NEW ANTIBODY DRUG CONJUGATE (ADC) WITH ERIBULIN IN TRIPLE NEGATIVE BREAST CANCER (TNBC) PATIENT-DERIVED XENOGRAFT (PDX)

#B107

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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 folate into cells. Overexpression of FRA may confer a growth advantage to tumors by increasing folate uptake and affect 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 TNBC (2). Due to an absence of potential 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 interrogated 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 xenograft (PDXs) recapitulate human tumor biology and 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.

In this study, MORAb-202, a novel folate receptor-targeting eribulin conjugate created through a Morphotek and Eisai collaboration, was tested in FRA-expressing TNBC PDXs and was compared to free eribulin.

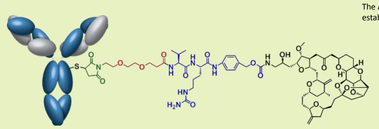
The national IMODI (Innovative MODels Initiative) consortium collection

Current IMODI PDX collection and initial objectives

Breast cancer repartition in clinic

PDX breast cancer collection (n=30)

MORAb-202 : antibody-drug conjugate (ADC*) consisting of farletuzumab paired with a cathepsin-cleavable form of eribulin.



The ADC described in this poster is investigational, as efficacy and safety have not been established. There is no guarantee that this ADC will be available commercially.

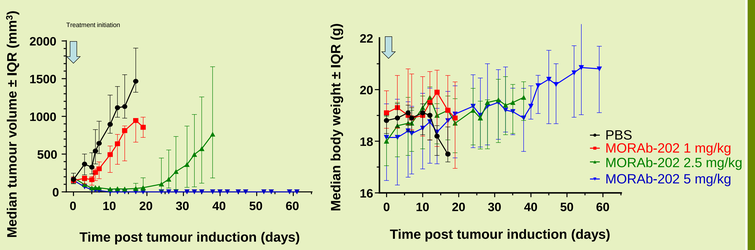
In vitro anti-proliferation activity

Crystal Violet assay; EC50 (nM)			
IGROV I (FRA +++)	NIH-OVCAR-3 (FRA++)	NCI-H2110 (FRA++)	A431-A3 (FRA +/-)
0.01	0.16	0.73	23

Highlights:

- Eribulin:MAb ratio of 4.0
- Low aggregate levels (< 1%)
- Highly cytotoxic to folate receptor (FRA)-positive cells and low levels of off-target killing
- Bystander effect in mixed tumor cell populations
- Serum-stable
- Highly efficacious in tumor cell xenograft models

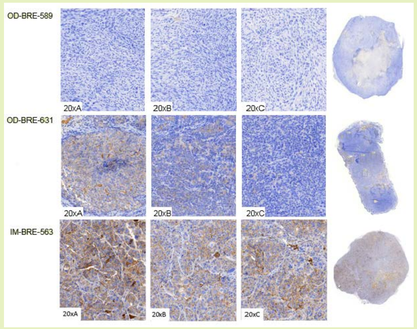
In vivo anti-proliferation activity
(CDX: NCI-H2110 FRA positive tumour)



RESULTS

IHC analysis

FRA expression



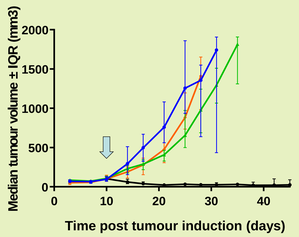
PDX characterization

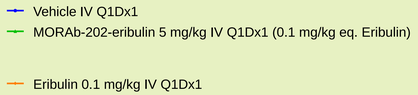
Patient derived tumor	Histological analysis of the tumor
OD-BRE-589	TNBC Spindle cells carcinoma ER(-), PR(-), HER2(-)
OD-BRE-631	TNBC invasive ductal carcinoma ER(-), PR(-), HER2(-)
IM-BRE-563	TNBC invasive ductal carcinoma ER(-), PR(-), HER2(-)

IHC analysis

OD-BRE-589 was negative for FRA.
A moderate (and heterogenous) to high expression of FRA was observed for OD-BRE-0631 and IM-BRE-563.

In vivo anti-proliferation activity
(PDX: OD-BRE-589 FRA negative tumour)





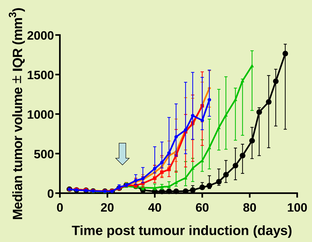
Group	Data	D28
Vehicle IV Q1Dx1	Median (mm³)	1257
	T/C%	100
MORAb-202 5 mg/kg Q1Dx1 (0.1 mg/kg eq. Eribulin)	Median (mm³)	656
	T/C%	52
Eribulin 0.1 mg/kg IV Q1Dx1	Median (mm³)	882
	T/C%	70
Eribulin 3.2 mg/kg IV Q1Dx1	Median (mm³)	25
	T/C%	2

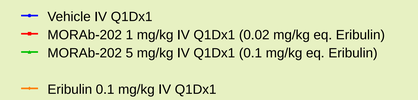
T/C%: *ratio* of the median tumour volume of treated group (T) versus vehicle treated group (C)

Antitumor efficacy

In FRA negative tumor, a marginal antitumor activity was observed for mice treated with MORAb-202.

In vivo anti-proliferation activity
(PDX: OD-BRE-631 FRA positive tumour)





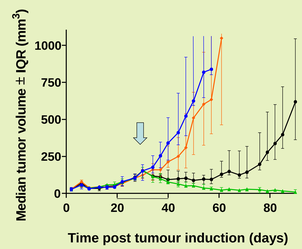
Group	Data	D60
Vehicle IV Q1Dx1	Median (mm³)	920
	T/C%	100
MORAb-202 1 mg/kg Q1Dx1 (0.02 mg/kg eq. Eribulin)	Median (mm³)	1104
	T/C%	120
MORAb-202 5 mg/kg Q1Dx1 (0.1 mg/kg eq. Eribulin)	Median (mm³)	413
	T/C%	45
Eribulin 0.1 mg/kg IV Q1Dx1	Median (mm³)	1115
	T/C%	121
Eribulin 3.2 mg/kg IV Q1Dx1	Median (mm³)	73
	T/C%	8

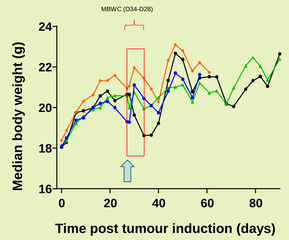
T/C%: *ratio* of the median tumour volume of treated group (T) versus vehicle treated group (C)

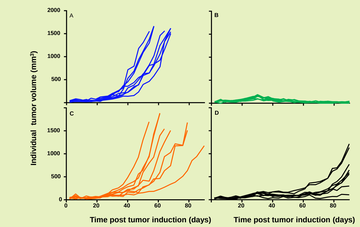
Antitumor efficacy

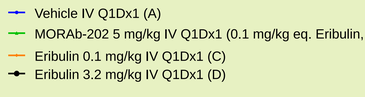
In FRA positive tumor, a significant antitumor activity was observed for mice treated with MORAb-202 at 0.1 mg/kg eq. eribulin. At equivalent dose, no antitumor activity was observed with eribulin without targeting vector.

In vivo anti-proliferation activity
(PDX: OD-BRE-589 FRA positive tumour)









Group	MBWC (D34-D28, %)
Vehicle IV Q1Dx1	5.4
MORAb-202 5 mg/kg Q1Dx1 (0.1 mg/kg eq. Eribulin)	0.8
Eribulin 0.1 mg/kg IV Q1Dx1	6.0
Eribulin 3.2 mg/kg IV Q1Dx1	-8.4

Group	Data	D57
Vehicle IV Q1Dx1	Median (mm³)	838
	T/C%	100
MORAb-202 5 mg/kg Q1Dx1 (0.1 mg/kg eq. Eribulin)	Median (mm³)	21
	T/C%	2
Eribulin 0.1 mg/kg IV Q1Dx1	Median (mm³)	1048
	T/C%	99
Eribulin 3.2 mg/kg IV Q1Dx1	Median (mm³)	94
	T/C%	11

T/C%: *ratio* of the median tumour volume of treated group (T) versus vehicle treated group (C)

Antitumor efficacy

In IM-BRE-563, a higher response was observed with MORAb-202 at 0.1 mg/kg Eq. eribulin when compared to mice treated with eribulin at 3.2 mg/kg. At this end of the experiment, all mice treated with MORAb-202 were tumor free.
A body weight loss was observed only for mice treated with eribulin at the highest dose.

Conclusions and perspectives

- FRA expression could be used for MORAb-202 activity biomarker,
- Antitumour activity of MORAb-202 is dependent of FRA expression,
- At equivalent dose MORAb-202 showed a higher antitumour activity when compared to free eribulin. In highly expressive FRA tumour, to observe similar antitumor activity 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.
- Triple-Negative Breast Cancer that does not express estrogen, progesterone 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 tumours.

References
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