ADCs optimization led to a significant anti-tumoral activity in lymphoma and breast tumor xenograft mouse models

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McSAF Chemical Tools for BioConjugation & BioDrugs

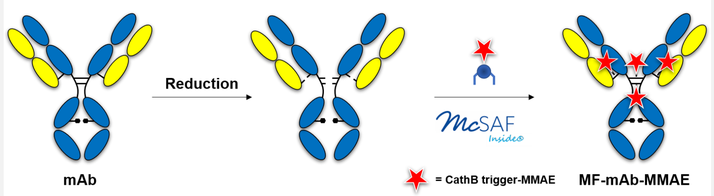
#4115

1 CONTEXT & OBJECTIVES

✓The Antibody Drug Conjugate (ADC) therapeutic encompasses a technology based on specificity with targeted antibody and cytotoxicity.

✓By using the specificity of the antibody, the ADC construct locally releases the drug on tumor cells expressing the antigen. Discovered twenty years ago, the ADC development has been limited by the off target cytotoxic delivery, due to the lack of control of the number of conjugated drugs per antibody and a stability of the linkage between the drug and antibody that can be improved.

✓McSAF is a deep tech company developing new chemical tools for bioconjugation, with core capabilities and know-how that span across the modification of payloads and proteins, along with the development of next-generation ADCs.



✓The development of state-of-the-art linkers allowing the functionalization and rebridging of disulfide bridges, instead of the attachment to a single cysteine performed in Adcetris®, led to enriched DAR 4 ADCs with a site-specific distribution of drug position on IgG1.

✓By using this new technology, the aim of the study was to demonstrate the efficacy and specificity of McSAF ADCs compared to standards of care with *in vitro* and *in vivo* experiments.

✓Firstly, the *in vitro* experiments compared the efficacy of two new ADCs (MF-TTZ-MMAE or MF-BTX-MMAE) to their standard of care reference, Kadcyla® (T-DM1) or Adcetris®.

✓Secondly, using xenograft tumor mice models, the two specific ADCs were tested on HER2 positive breast tumor model (BT-474 cell line) and on CD30 positive Non Hodgkin's Lymphoma tumor model (Karpass-299 cell line).

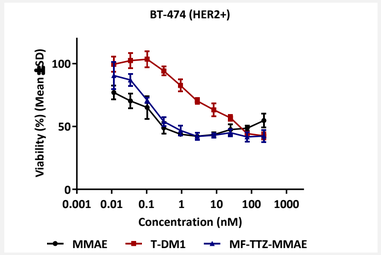
✓The cell injection was performed subcutaneously and the groups were randomized when tumors volume reached a mean value between 100-200 mm^3. Mice received IV injection once or twice. Mice were monitored for several weeks for their body weight and tumor volume.

2 RESULTS

✓ *IN VITRO* EXPERIMENTS

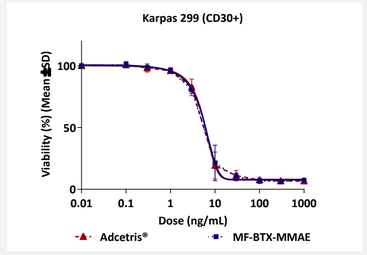
Determination of cytotoxicity of McSAF ADCs compared to standard of care (SOC).

Viability after 72 h



✓Cytotoxicity of **MF-TTZ-MMAE** (IC_{50} = 0.57 nM) was higher than **T-DM1** (IC_{50} = 45.78 nM) and similar to **MMAE** (IC_{50} = 0.29 nM) on HER2-positive cells.

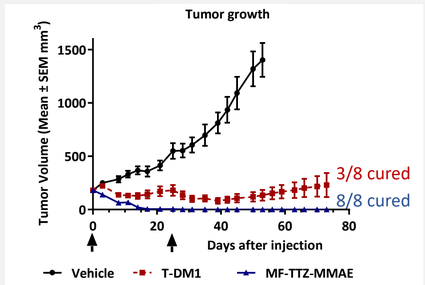
Viability after 96 h



✓Cytotoxicity of **MF-BTX-MMAE** (IC_{50} = 0.104 nM) was similar to **Adcetris®** (IC_{50} = 0.105 nM) on CD30-positive cells.

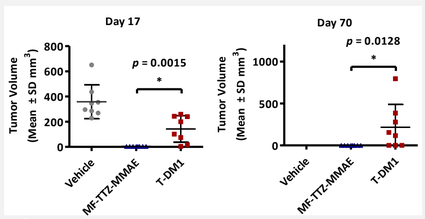
✓ *IN VIVO* EXPERIMENTS

Assessment of **MF-TTZ-MMAE** and **T-DM1** efficacy on nude mice bearing BT-474 tumor.

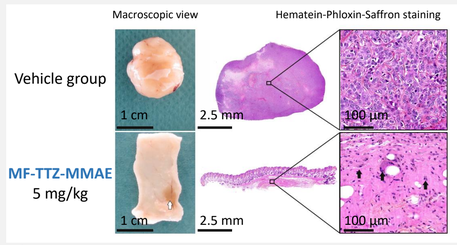


Treatment	Dose	Route	Schedule
Vehicle	-	IV	Q1Dx2
T-DM1	5 mg/kg	IV	Q1Dx2
MF-TTZ-MMAE	5 mg/kg	IV	Q1Dx2

Mice received two IV injections of the compounds.



✓Tumor regression was observed for all mice treated with **MF-TTZ-MMAE** from D17, while only 3 out of 8 mice treated with **T-DM1** loss their tumor at the end of the study.



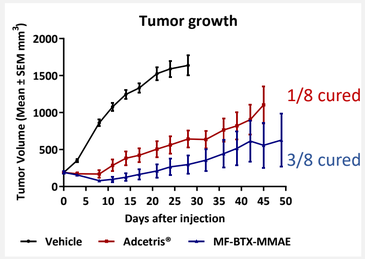
✓Tumor well established with numerous-malignant cells in Vehicle group.
✓No tumor left and at tumor injection site, no HER2 residuals cells in **MF-TTZ-MMAE** treated group.

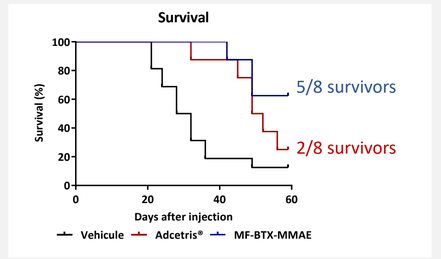
✓ *IN VIVO* EXPERIMENTS

Assessment of **MF-BTX-MMAE** and **Adcetris®** efficacy on SCID mice bearing subcutaneous Karpas-299 tumor.

Treatment	Dose	Route	Schedule
Vehicle	-	IV	Q1Dx1
Adcetris®	0.5 mg/kg	IV	Q1Dx1
MF-BTX-MMAE	0.5 mg/kg	IV	Q1Dx1

Mice received one IV injection of the compounds.





✓**MF-BTX-MMAE** induced stronger tumor growth inhibition (T/C% = 9%) than **Adcetris®** (T/C% = 42%).
✓Treatment with **MF-BTX-MMAE** led to a better survival, with 5 animals still alive at the end of the study.

3 CONCLUSION

✓The McSAF's bioconjugation technology provides a new tool to generate strong ADCs with high stability and efficacy.

✓Tested on two mice bearing tumor models, the ADC treatment, in comparison with SOC, revealed better efficacy and in some cases succeeded to cure the animals.

✓This work will be completed with the determination of the therapeutic index and the pharmacokinetic profile of McSAF's ADCs.

✓ **McSAF's technologic platform**
- DAR 4 validated
- DAR 2 ongoing
- DAR 1 ongoing

✓ **4 patents**
- Technology
- CD30
- HER2
- CD56

McSAF is happy to talk about potential synergistic partnership integrating these technologies.

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