ABSTRACT
#2670

Combination of anti-HER2 ADC XMT-1522 and checkpoint inhibitor pembrolizumab for treatment of NSCLC in preclinical models

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Summary

The combination of antibody-drug conjugates (ADCs) and immunomodulatory cancer therapies is emerging as a powerful strategy for cancer treatment. Tumor-targeted delivery of a cytotoxic payload capable of inducing immunogenic cell death (ICD) can trigger both an innate and an adaptive immune response, whereby increased recruitment of effector T-cells to the tumor and formation of tumor specific immunological memory can result in a durable treatment response.

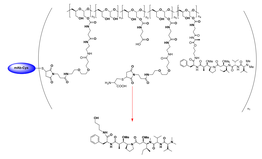
We have characterized the ability of both the free payload AF-HPA and the anti-HER2 ADC XMT-1522 to induce ICD in vitro in multiple cell lines (NCI-N87, HT-29, SKBR3), as measured by the cell surface expression of the ICD marker calreticulin (CRT) by microscopy and flow cytometry (FACS) and ATP release.

XMT-1522 as a single agent induced significant tumor regressions in two patient-derived xenograft (PDX) models of HER2-expressing non-small cell lung cancer (NSCLC).

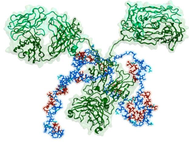
The combination of XMT-1522 with the checkpoint inhibitor pembrolizumab was tested in patient-derived xenograft (PDX) models of HER2-expressing non-small cell lung cancer (NSCLC) in a mouse with a humanized immune system. Expression of huPD-L1 in the tumor was confirmed by FACS and immunohistochemistry (IHC). Lymphocyte sub-populations were quantified in whole blood and in tumor by FACS and IHC.

The combination of XMT-1522 with pembrolizumab resulted in a better response than either of the two monotherapies. These data provide a rationale for XMT-1522 to be tested clinically as a single agent in HER2-expressing NSCLC, as well as a rationale for combination of XMT-1522 and immunomodulatory therapies in NSCLC.

XMT-1522 ADC Structure and Drug Release



Auristatin F-HPA

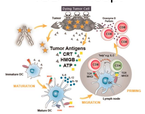


Green = mAb, Blue = Fleximer polymer;
Red = XMT-1267 (AF-HPA payload)

The anti-HER2 ADC XMT-1522 consists of a novel human IgG1 anti-HER2 monoclonal antibody and a novel, auristatin-based cytotoxic payload (Auristatin F-hydroxypropylamide, AF-HPA). An average DAR of 12 AF-HPA molecules is achieved via a biodegradable polymer conjugation platform.

Introduction

ICD Concept



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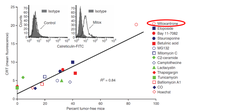
ICD inducers are well defined



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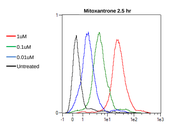
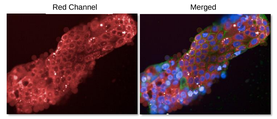
Calreticulin Translocation to the Cell Surface

Mitoxantrone Induces Dose Dependent Calreticulin Exposure on NCI-N87 cells

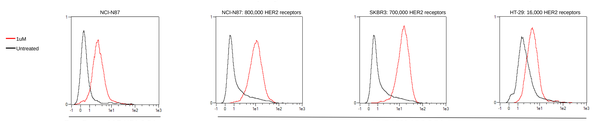




Red – Calreticulin
Green – Membrane
Blue - Hoechst

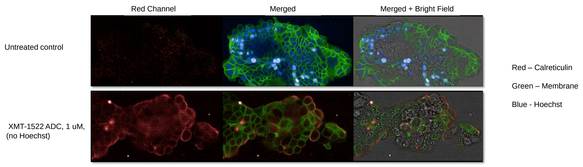
Live Cell Images 24 hr, 20x

XMT-1522 ADC and free payload AF-HPA Induces Calreticulin Exposure



Free Payload AF-HPA 2.5 hr

XMT-1522 ADC 2.5 hr



Red – Calreticulin
Green – Membrane
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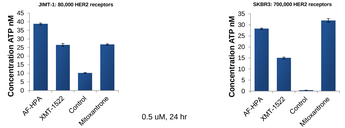
Live NCI-N87 Cell Images 24 hr, 20x

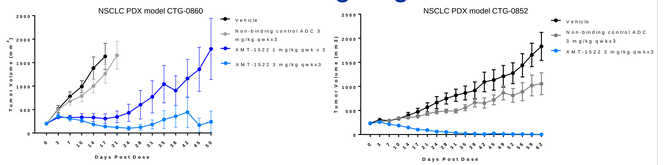
ATP release

XMT-1522 ADC and free payload AF-HPA Induces ATP release



0.5 uM, 24 hr

XMT-1522 as a single agent in vivo



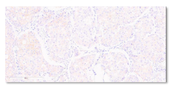
XMT-1522 pembrolizumab combo in vivo

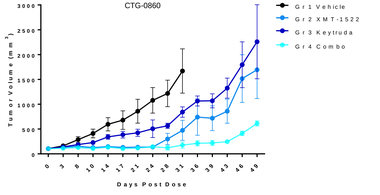
Study Design: Humanized Mouse*/CTG-0860 NSCLC PDX Model

Groups	Test Agent	Dose (mg/kg)	Schedule	N of mice
1	Vehicle			5
2	XMT-1522	1mg/kg	iv qwk x 3	5
3	Keytruda (PD-1)	2.5 mg/kg	Ip q5d x 6	5
4	XMT-1522 + Keytruda	1 mg/kg + 2.5 mg/kg	iv qwk x 3 + Ip q5d x 6	5

*Unmatched HLA Humanized CD34+ engrafted Immune compromised female mice (Taconic NOG) between 5-8 weeks

HER2 expression IHC



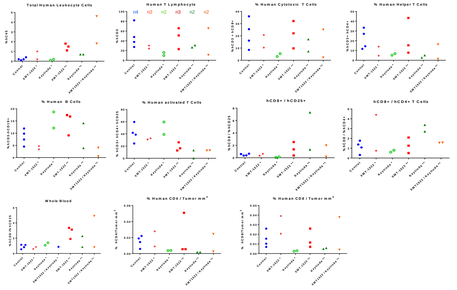


TILs Analysis in Tumor

Markers analyzed by FACS
- Mouse and human CD45
- Infiltrating lymphocytes:
  - hCD3 (T cells)
  - hCD4 (helper T cells)
  - hCD8 (cytotoxic T cells)
  - hCD19 (B cells)
- T cells activation and proliferation:
  - hCD25

* Tumors were analyzed at the time when control group reached endpoint

** Tumors were analyzed at the study end



Discussion and Conclusions

- The free payload AF-HPA and the ADC XMT-1522 both induce ICD in vitro as evidenced by at least two well established ICD markers:
  - the cell surface expression of calreticulin, CRT, usually contained in the lumen of the endoplasmic reticulum, translocated to the cell surface within a few hours after treatment with AF-HPA or XMT-1522 alone
  - ATP release was confirmed after treatment with AF-HPA or XMT-1522
- XMT-1522 as a single agent induced significant tumor regressions in two patient-derived xenograft models of HER2-exressing non-small cell lung cancer at a dose of 3 mg/kg once weekly for 3 weeks
- The combination of XMT-1522 with the checkpoint inhibitor pembrolizumab resulted in a better response than either of the two monotherapies in patient-derived xenograft models of HER2-expressing non-small cell lung cancer in a mouse with a humanized immune system
- There was no clear correlation in TILs and tumor response
- The data provide a rationale for XMT-1522 to be tested clinically as a single agent in HER2-expressing NSCLC, as well as a rationale for combination of XMT-1522 and immunomodulatory therapies in NSCLC

References

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Acknowledgements

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