ON203: A new antibody targeting the oxidized form of macrophage migration inhibitory factor demonstrates antitumorigenic activity in preclinical models

ENA 2022 EORTC NCI AACR 34th Symposium

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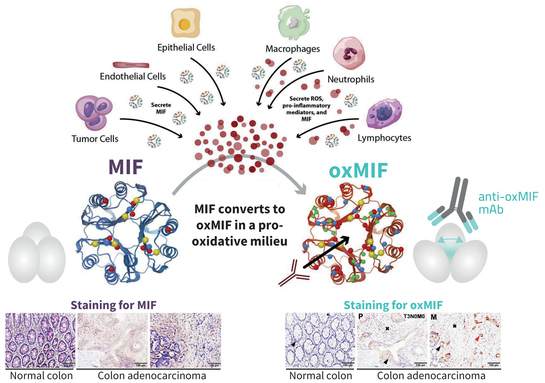
1 Introduction

Macrophage migration inhibitory factor (MIF) is a pleiotropic, pro-inflammatory cytokine that promotes tumorigenesis and is able to modulate the tumor microenvironment (TME) to immune evasive, and immune tolerant phenotypes. Overexpression of MIF in tumor tissue is associated with poor prognosis. MIF distinguishes from other cytokines and chemokines due to its constitutive expression and high presence in circulation of healthy subjects at levels of ~6 ng/ml [1-9].

MIF has proven undruggable by antibodies and small molecules

The founders of OncoOne discovered that MIF occurs in two immunologically distinct conformational isoforms, termed reduced MIF (redMIF) and oxidized MIF (oxMIF) [10]. RedMIF is the abundantly expressed isoform of MIF [10-12]. In contrast, oxMIF is the disease-related isoform that was specifically detected in solid tumors [10-12]. The redox-dependent MIF structure modifications modulate enzymatic and biological functions and enables binding of anti-oxMIF antibodies [13,14]. A first generation IgG1 anti-oxMIF antibody (mAb), imalumab, was investigated in Phase 1 (NCT01765790) and Phase 2 studies, in patients with CRC (NCT02448810) and ovarian cancers (NCT02540356) revealing that imalumab was well tolerated and showed signs of efficacy [15]. However, these studies were terminated prematurely [15].

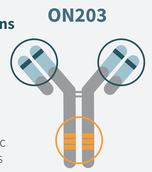
oxMIF – the disease-related and druggable isoform of MIF



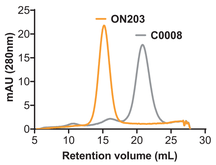
2 Antibody Engineering & Biochemical Properties

Optimized variable domains
Improved biophysical and pharmacological properties

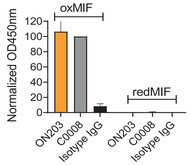
Optimized Fc
Engineered Fc to enhance Fc mediated effector functions



Hydrophobicity (HIC)



Specificity (ELISA)



Affinity (SPR)

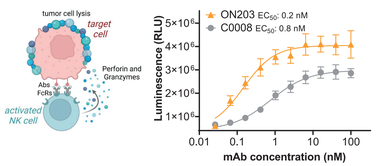
	C0008	ON203
K_D , nM (SD)	3.5 (0.4)	6.1 (2.3)

ON203 demonstrated highly improved biochemical properties compared to C0008, while retaining the low nM affinity to oxMIF

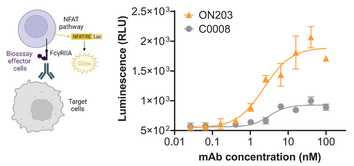
C0008, is a mAb produced in our lab with the identical sequence as imalumab but devoid of the C-terminal Lys

3 *In vitro* efficacy and safety

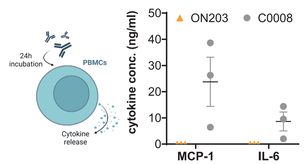
ADCC assay



ADCP reporter assay

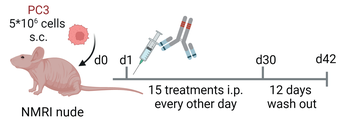


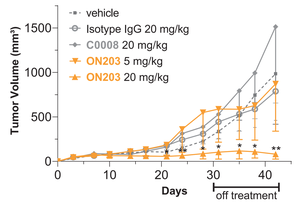
Cytokine release from PMBCs

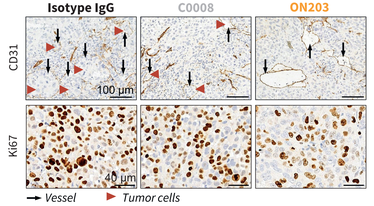


***In-vitro* efficacy is increased up to 10-fold for ON203 compared to C0008, but no unspecific cytokine release is observed**

4 *In vivo* efficacy – PC3 Xenograft Model



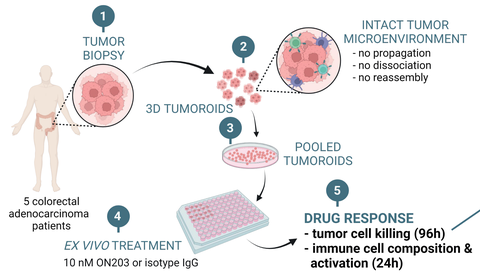




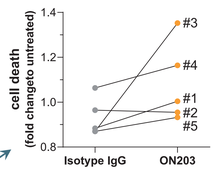
NMRI nude mice were subcutaneously injected with PC3 human prostate cancer cells. One day after tumor cell implantation mice were treated every other day with ON203, C0008, Isotype IgG or vehicle as indicated. Absolute tumor volume is plotted over time (median ± interquartile range, n=9 /group), ANOVA with Dunnett's multiple comparisons test on log transformed data was used, *p ≤0.05; **p ≤0.01, ON203 20mg/kg vs. vs. vehicle + Isotype IgG

ON203 exerts superior *in vivo* efficacy in a prophylactic mouse model of prostate cancer compared to C0008

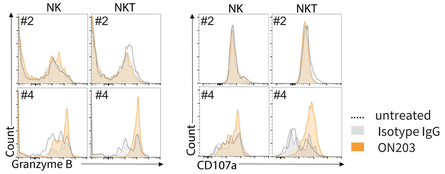
5 *Ex vivo* efficacy – Colorectal Cancer Tumoroids



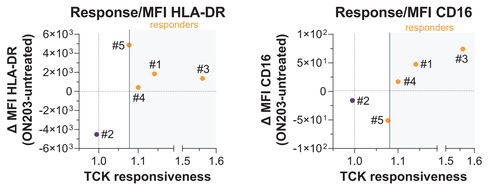
Tumor Cell Killing (TCK)



Activated NK and NKT cells



Activated Macrophages



- **4 out of 5 CRC tumoroids responded with tumor cell killing**
- **Tumor cell killing correlates with activated effector cells in responders**
  - NK/NKT (↑activation and degranulation markers Granzyme B and CD107a)
  - Macrophages (↑HLA-DR and CD16)

6 Conclusions

oxMIF, the disease-related and druggable isoform of MIF, is a novel target with broad applications in cancer therapy. Our results demonstrate direct antitumorigenic effects of the anti-oxMIF antibody ON203 (i) by blocking the biologic function of oxMIF thereby reducing tumor cell proliferation and angiogenesis and (ii) by immunomodulation of the tumor microenvironment. In the upcoming Phase 1 trial we will evaluate ON203's safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with solid tumors. ON203 bears a high potential as a standalone therapy or in rational combinations with immune checkpoint inhibitors or antiangiogenic agents in the treatment of solid tumors.

References

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