ON203: A new antibody targeting the oxidized form of macrophage migration inhibitory factor (oxMIF) demonstrates antitumorigenic activity and TME modulation in patient-derived CRC tumoroids

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1 Introduction
Macrophage migration inhibitory factor (MIF) is a pleiotropic, pro-inflammatory cytokine which can directly promote 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.\(^1\)\(^-\)\(^13\) MIF is considered undruggable by antibodies and small molecules.

The founders of OncoOne discovered that MIF occurs in two immunologically distinct conformational isoforms, termed reduced MIF (reMIF) and oxidized MIF (oxMIF).\(^1\)\(^4\)-\(^1\)\(^9\) The rebox-dependent MIF structure modifications affect enzymatic and biological functions.\(^1\)\(^4\)-\(^1\)\(^9\) reMIF is the abundantly expressed isoform, whereas oxMIF is the disease-related isoform specifically detected in solid tumors.\(^1\)\(^4\)-\(^1\)\(^7\) A first generation IgG1 anti-oxMIF antibody, imalumab, was investigated in Phase 1 (NCT01765790) and Phase 2 studies in patients with CRC (NCT02540256) and ovarian cancers (NCT02488103) demonstrating that imalumab was well tolerated and showed signs of efficacy. These studies were terminated prematurely.\(^1\)\(^6\)

2 ON203 – optimized targeting of oxMIF

OncoOne’s novel and improved anti-oxMIF antibody
Optimized variable domains
Improved biophysical and pharmacological properties
Optimized Fc
Engineered Fc to enhance Fc-mediated effector functions
- reduced aggregation
- enhanced ADCC
- superior efficacy in solid tumor xenograft models

3 Method: Freshly isolated 3D CRC tumoroids treated with ON203

4 CRC patient characteristics

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5 Tumoroid composition

Immune cell composition of colorectal adenocarcinoma tumoroids (determined by flow cytometry; gated on single live CD45+ cells (5–40x10⁶ cells; CD8+ T (CD3+CD8), CD4+ T (CD3+CD4), NK (CD3-CD56), NKT (CD3-CD56), macrophages (CD3-CD68), other CD45+ cells containing e.g. myeloid cells and B cells).

6 ON203-induced tumor cell killing (TCK)

Cell viability decreased 96h post-treatment by high-content 3D computational bioimaging.

7 oxMIF and immune cells: ON203 activates effector cells

8 Conclusions & Outlook

- MIF is a pivotal regulator of innate and adaptive immunity with a wide range of therapeutic applications in oncology
- Drugging the disease-related isoform oxMIF is the key for drugging MIF
- Re-engineering of the first generation anti-oxMIF mAb imalumab led to ON203
- improved physicochemical properties (hydrophobicity, aggregation)
- improved efficacy in in vitro cancer models
- Efficacy proven in primary CRC tumoroids: tumor cell killing and activation of effector cells
- ON203 has a high potential for combinations with angio genesis- and immune checkpoint-inhibitors

Lead candidate ON203 is on track to enter clinical phase I by Q1 2023

References