Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of the Anti-oxMIF Antibody ON203 in Malignant Solid Tumors

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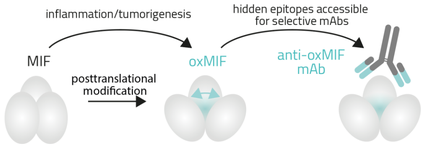
1 Introduction

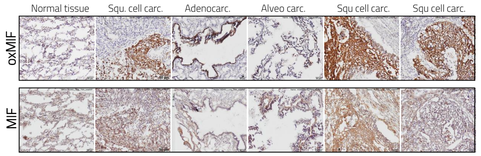
Macrophage migration inhibitory factor (MIF) is often described as a pleiotropic cytokine whose overexpression is associated with tumor aggressiveness, metastases, and poor prognoses. Due to its ubiquitous nature, MIF is considered an unsuitable target for therapeutic intervention. [1-10]

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).[11] The redox-dependent MIF structure modifications affect enzymatic and biological functions[12]. RedMIF is the abundantly expressed isoform, whereas oxMIF is the disease-related isoform specifically detected in solid tumors[11-13]. Analysis of oxMIF in normal lung and lung cancer tissue showed a distinct staining in tumor tissue - most pronounced in adenocarcinoma and squamous cell carcinoma (both NSCLCs). In contrast, total MIF showed a more uniform staining in tumor as well as in the normal lung cores [11,14].

oxMIF – the disease-related and druggable isoform of MIF





Schinagl et al, 2015

2 First Generation Anti-oxMIF Antibody in Phase 1

A first-generation anti-oxMIF monoclonal antibody (mAb), **imalumab**, was able to demonstrate an **acceptable safety profile** and **signs of efficacy in a Phase 1 clinical trial** (NCT01765790) in patients with malignant solid tumors, seven of which were patients with NSCLC. After treatment, eight patients showed signs of stable disease of greater than 4 months. When evaluating tumor types that had **prolonged stable disease**, **patients with immune-responsive tumors such as NSCLC**, ovarian and oesophageal appeared to benefit [15]. However, **Phase 1/2 studies with imalumab were terminated** prematurely[15].

3 ON203 – Optimized Human mAb Targeting oxMIF

ON203

OncoOne's novel and improved anti-oxMIF antibody

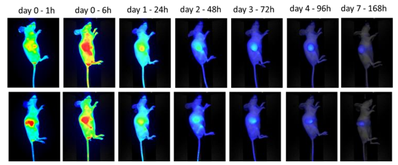
Optimized variable domains

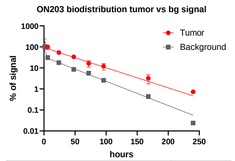
- ON203 specifically binds oxMIF with high affinity in the low nM range.
- Improved biophysical and pharmacological properties compared to imalumab.

Optimized Fc domain

- ON203 was engineered to enhance Fc-mediated effector functions
- IgG1/2 hybrid constant heavy chain with mutations increasing the affinity to FcγRIIIA and FcγRIIA

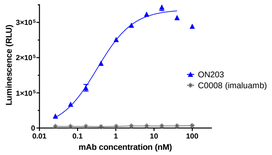
Biodistribution in a Xenograft Tumor Model





	Tumor	Background
Initial Half Life (Fast)	13.8	1.2
Terminal Half Life (Slow)	64.7	27.2

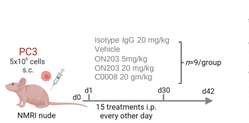
ADCC reporter assay

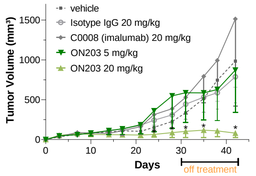


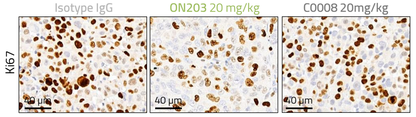
- Tumor accumulation and retention of ON203 for at least 7 days in a xenograft mouse model
- Enhanced ADCC and ADCP activity in the presence of oxMIF presenting target cells

5 Efficacy in a Xenograft Tumor Model

Prophylactic model







Treatment with ON203 in a PC3 prostate cancer xenograft tumor model decreased the proliferation markers Ki67.

Treatment with ON203

- suppresses tumor growth
- is superior to imalumab
- reduces tumor proliferation

6 FIH Study – Clinical Trial Synopsis

Dose escalation phase

ON203 (Q2W)

0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
				3 subjects
			3 subjects	
		3 subjects		
	3 subjects			
3 subjects				

Dose expansion phase

ON203 (Q2W)
Biological active dose
18 subjects

Category	Phase 1
Study title	A Phase 1 open-label study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of the anti-oxMIF antibody ON203 in subjects with malignant solid tumors
Intervention	Dose escalation phase in 5 dosing groups, 0.3, 1, 3, 10, and 30 mg/kg ON203 Q2W, of 3-6 participants each according to 3+3 design Dose expansion phase with a selected dose in 18 patients with selected solid tumors
Patients number	n=15 in the dose escalation phase (if MTD is not reached) n=18 in the dose expansion phase
Key inclusion criteria	• Males and females ≥ 18 years • Patients with confirmed malignant solid tumor who are either refractory to, have failed, or refused standard treatments • ECOG performance status ≥ 1 • Anticipated life expectancy > 4 months at the time of screening
Primary outcome measures	Number and severity of adverse events and their causal relationship to ON203 according to the NCI CTCAE toxicity grade; Occurrence of dose limiting toxicities (DLTs)
Key secondary outcome measures	• Define PK parameters (e.g. maximum concentration (Cmax), minimum concentration (Cmin), area under the concentration vs time curve (AUC), half-life ($t^1/_2$), clearance (CL)) on different occasions • Progressive free survival (PFS) in months as defined by RECIST 1.1 criteria • OS, DCR, DOR, ORR
Exploratory outcome measure	• Levels of total and oxMIF in the circulation • Number of subjects who develop anti-drug antibodies • Levels of cancer cells (cancer cell DNA) in circulation • Analysis of immune contexture (cell populations/activation) before and after the treatment from tumor biopsies (where applicable) • IHC analysis of oxMIF and ON203 in tumor biopsies during treatment • Levels of other biomarkers in tumor tissue • MIF gene polymorphism
Estimated study duration	Dose escalation phase: est. 8 months, dose expansion Phase 12 months Treatment will continue until disease progression (increase of tumor volume by 20 %), unacceptable toxicity, dose-limiting toxicity, or withdrawal of consent
Allocation	U.S., 1-3 sites

6 Take Home Message

- oxMIF is a **pivotal regulator** of innate and adaptive immunity and is **highly expressed in lung cancer.**
- Anti-oxMIF ON203 has a high potential for immunotherapy in **combinations with checkpoint-inhibitors.**

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

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