

Targeting the oxidized form of macrophage migration inhibitory factor (oxMIF) with antibody ON203 activates the tumor microenvironment

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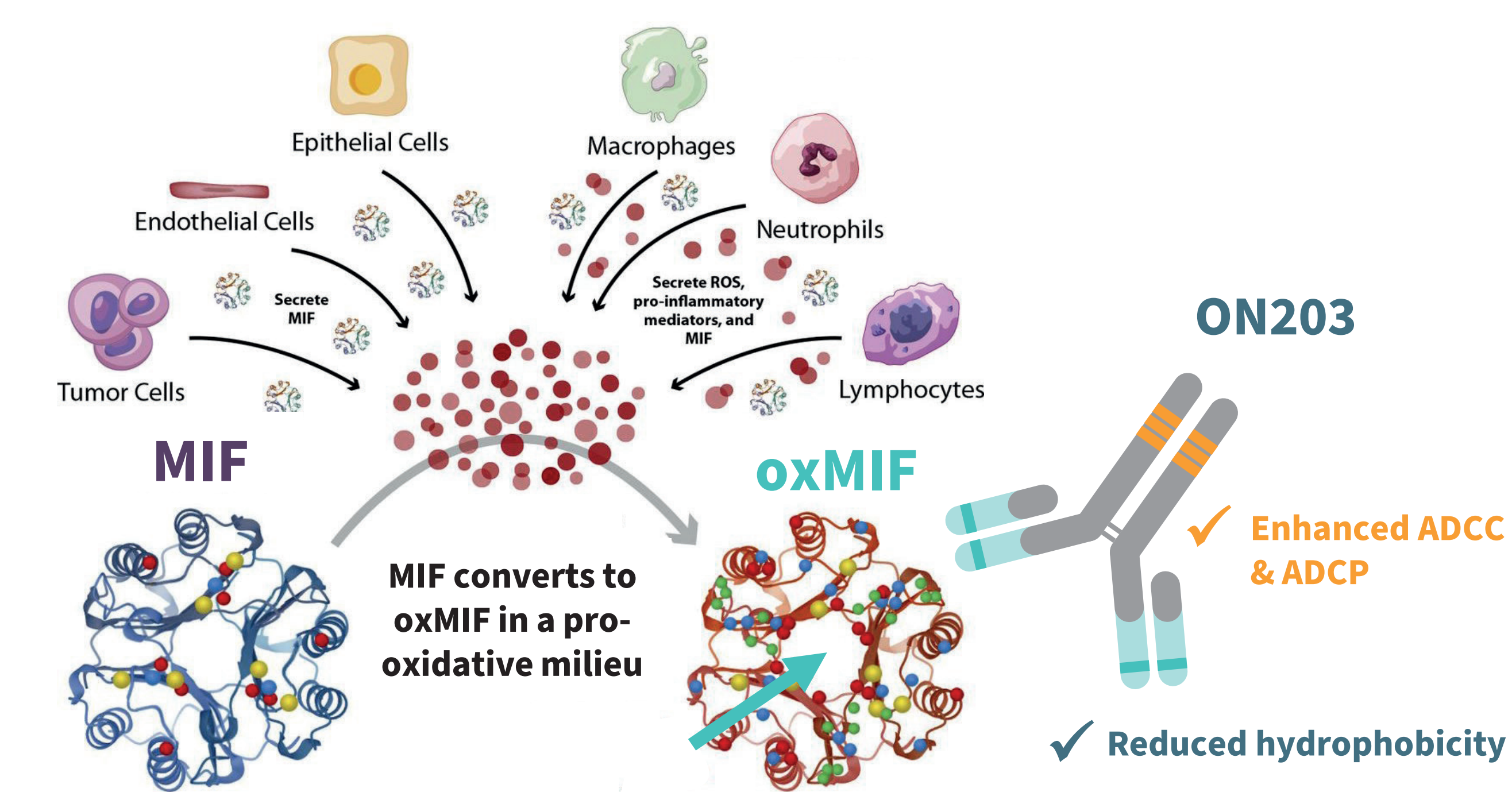


1 Introduction

Activation of the immunosuppressive tumor microenvironment (TMEs) can enhance immunotherapy response rates in solid cancers. One of the key TME regulators is the macrophage migration inhibitory factor (MIF). In addition to MIF's role in tumor cell proliferation, angiogenesis and metastasis, high levels of MIF induce the polarization of macrophages to the tumor enhancing M2-like subtype, suppresses cytotoxic T cells and correlates with poor response to immune checkpoint therapy¹⁻³. Therapeutic interventions targeting MIF directly are hampered due to MIF's ubiquitous expression and non-pathological roles.

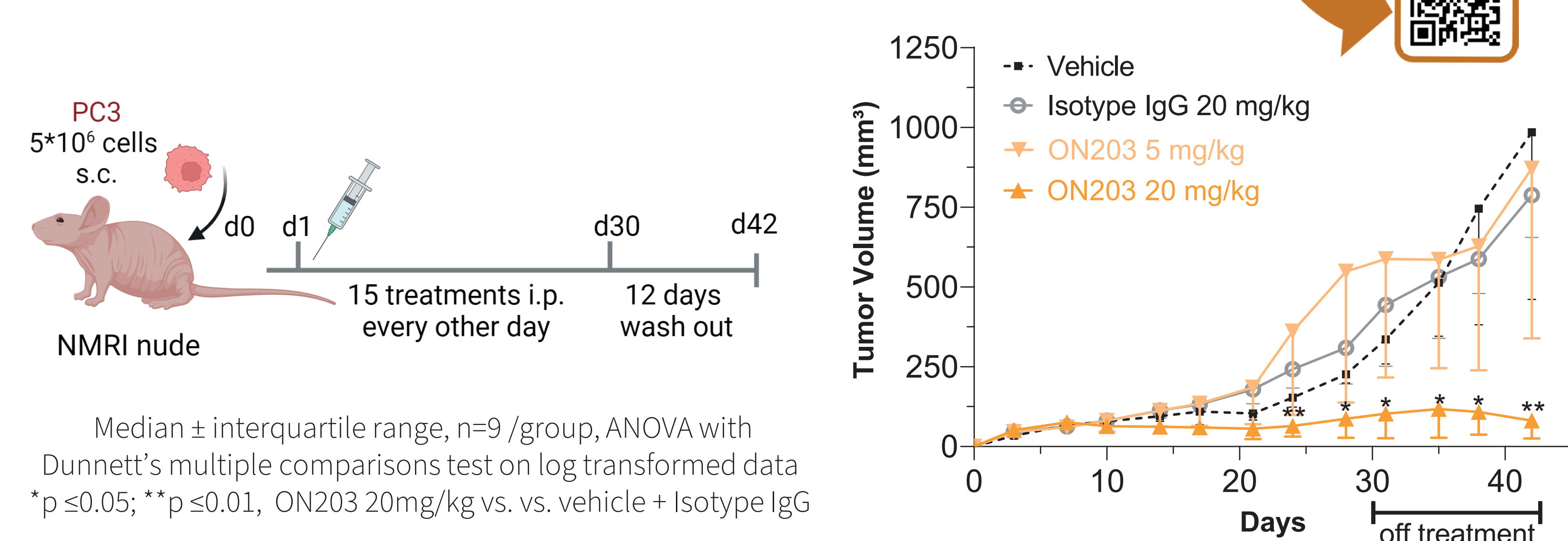
In contrast, the disease-related structural isoform of MIF⁴⁻⁶, termed oxMIF, is exclusively present in solid tumor tissue⁷ and can be specifically targeted by the novel anti-oxMIF antibody ON203. Neutralizing oxMIF with ON203 blocks the pro-tumorigenic activities historically attributed to MIF⁸⁻⁹.

➡ oxMIF is the disease-related and druggable isoform of MIF



Adapted from Thiele, Donnelly & Mitchell, JTC, 2022⁸

3 In vivo efficacy – PC3 Xenograft Model⁹

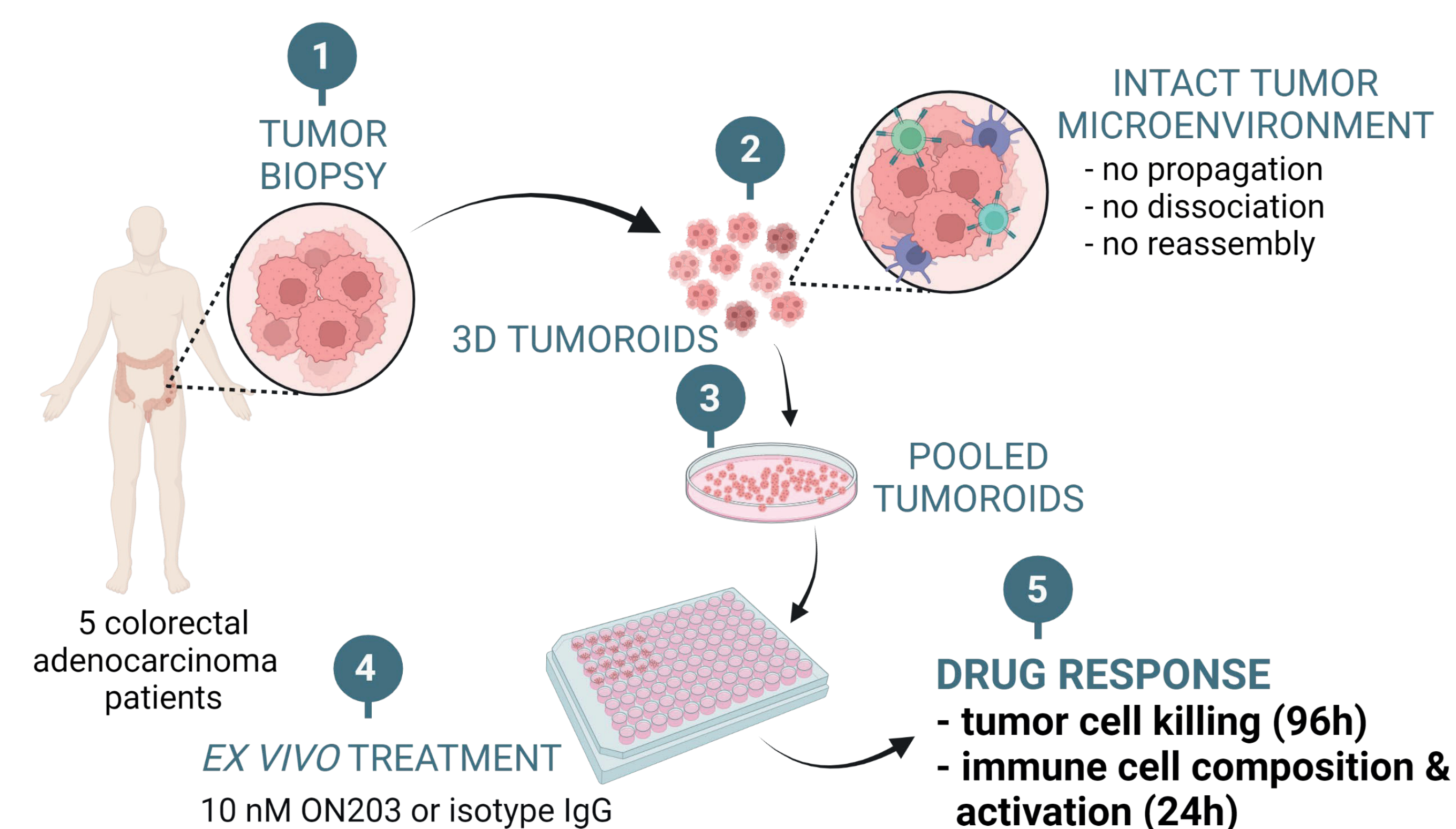


ON203 exerts significant tumor suppression upon treatment and maintains a durable effect after treatment ends

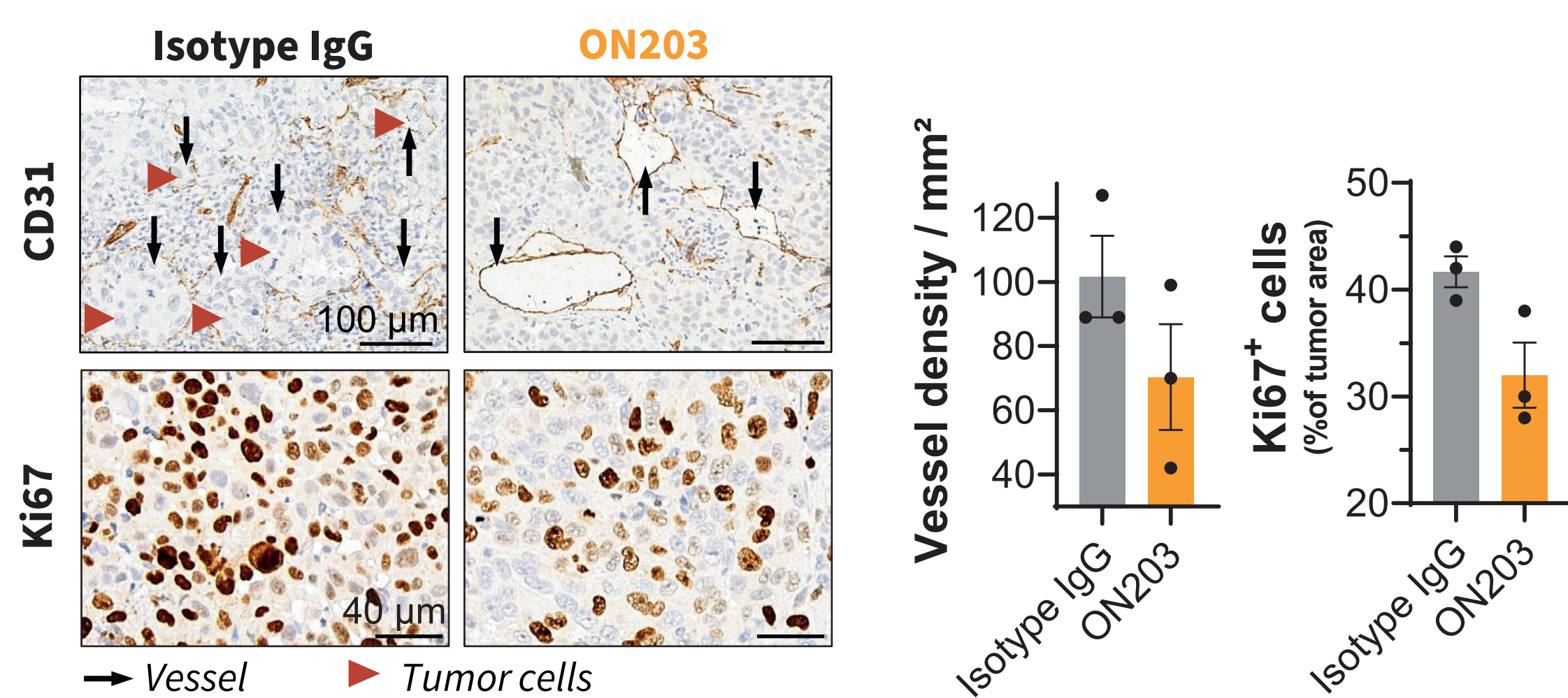
2 Methods

We determined the antitumorigenic and TME-modifying potential of the novel oxMIF-specific antibody ON203 in preclinical models including a xenograft mouse model and freshly isolated tumoroids from colorectal adenocarcinoma (CRC) patients retaining an intact TME. ON203-induced TME modulation and tumor cell killing were assessed by high-content 3D computational bioimaging, secretome analysis and flow cytometry.

To further characterize the immune population differences between treatment conditions, we employed multi-parameter clustering (FlowSOM/XShift) and compared the abundance of each cluster across conditions. Finally, we used dimensionality reduction (UMAP) to comparatively visualize the clusters in responding vs. non-responding tumoroids.

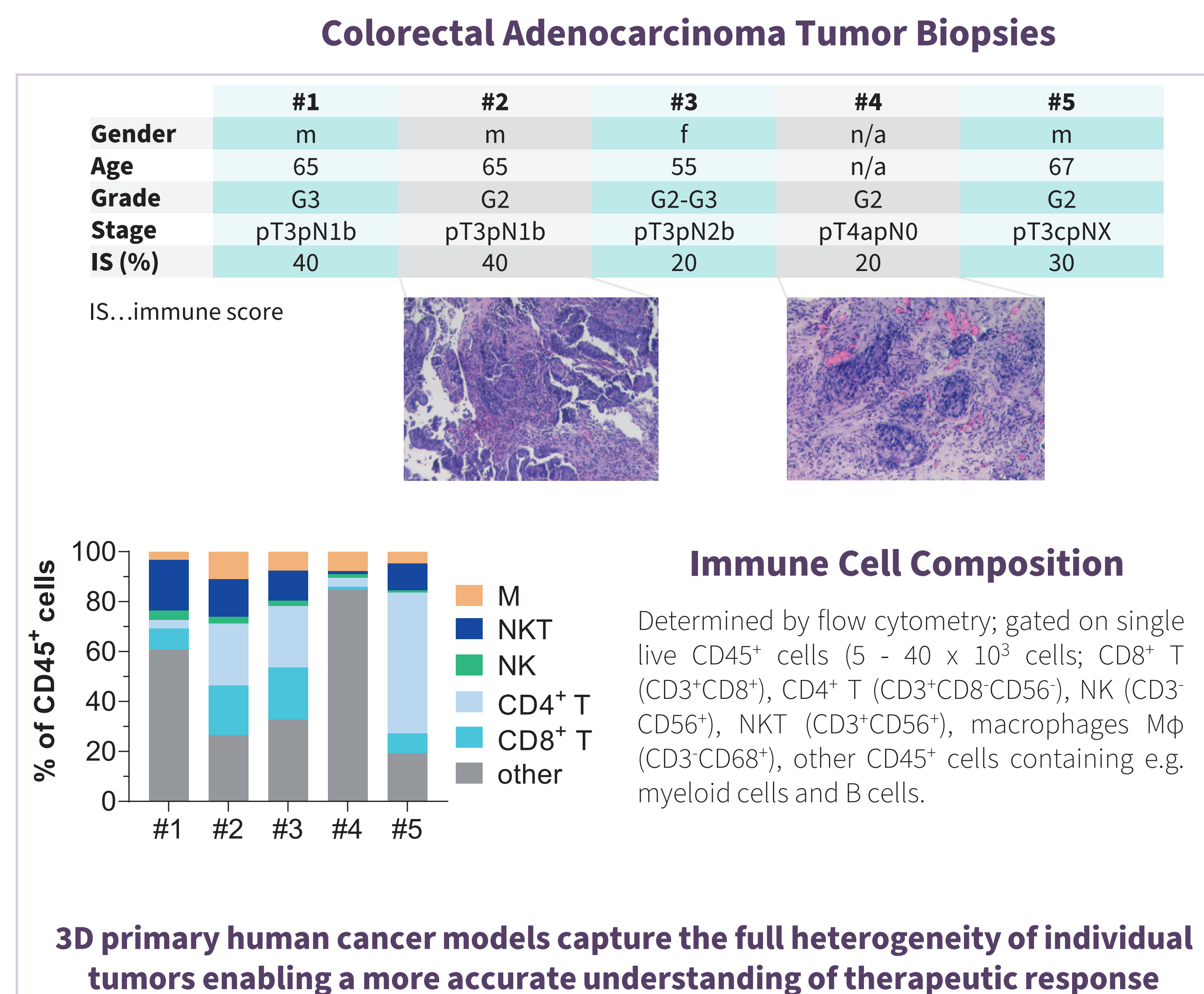


to check out our MCT First Disclosure Article on ON203 efficacy published today

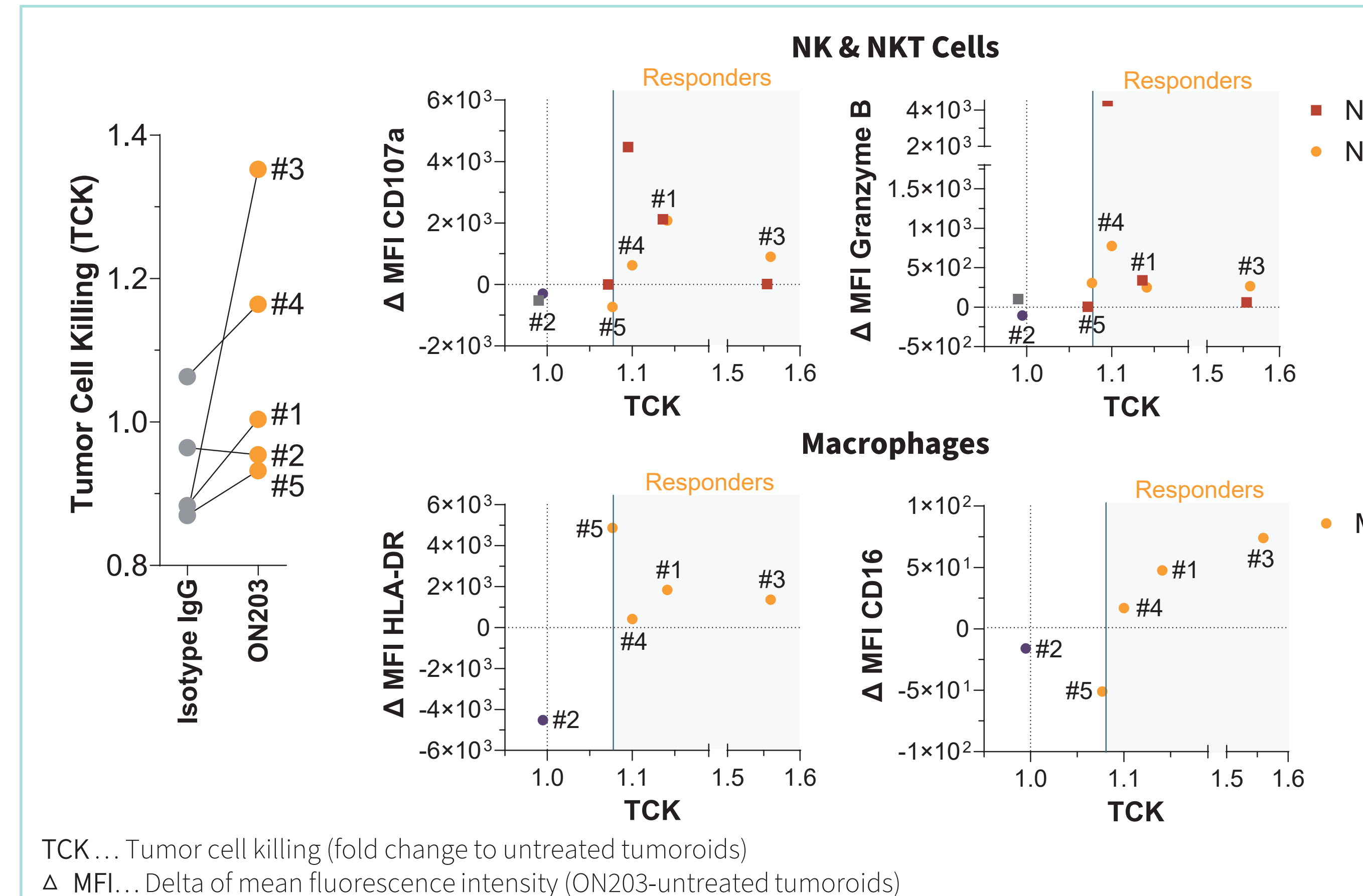


ON203 reduces proliferation and intravasation of tumor cells as well as vascularization, thereby reducing metastases

4 Ex vivo efficacy – Colorectal Cancer Tumoroids

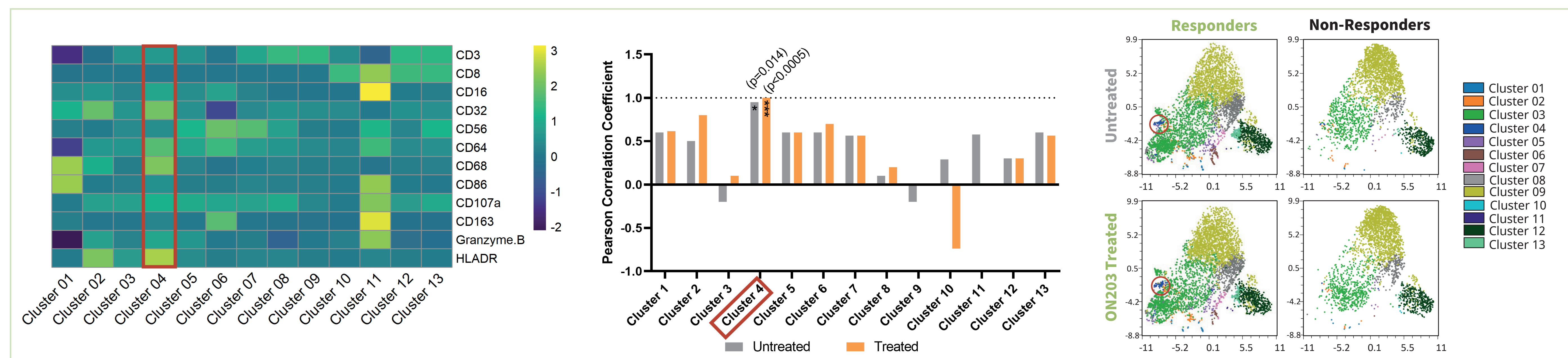


Tumor Cell Killing & Effector Cell Activation



4 out of 5 CRC tumoroids responded with tumor cell killing (TCK) and TCK correlates with effector cell activation

Multi-parameter Clustering & Correlation with Tumor Cell Killing



5 Conclusions

- ✓ ON203 significantly inhibited tumor growth and reduced proliferation and intravasation of tumor cells in this mouse xenograft model
- ✓ Four out of five CRC tumoroids responded to single agent ON203 with enhanced tumor cell killing (TCK) and immune cell activation
 - ON203 activated NK and NKT cells through the upregulation of Granzyme B and CD107a)
 - ON203 supported macrophage activation and repolarization to the anti-tumor M1-like phenotype via the upregulation of CD16 and HLA-DR, which was confirmed by unbiased multi-parameter cluster analysis
- ✓ These findings point to ON203 having a high potential for enhancing efficacy in combination with angiogenesis and checkpoint-inhibitors

References

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