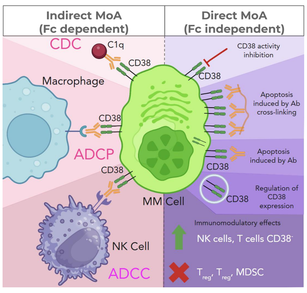
Ex Vivo Testing Platform Unveils Differential Response to Daratumumab and Isatuximab in Multiple Myeloma

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Introduction

Therapeutic antibodies have become essential tools for treating patients with Multiple Myeloma (MM). Daratumumab (Dara) and Isatuximab (Isa) are monoclonal antibodies (mAbs) that target CD38 and exhibit pleiotropic mechanisms of action. While it is widely recognized that Dara and Isa differ in their mechanisms of cell killing, the impact of these functional differences on therapeutic outcomes for different patients remains unclear. Therefore, there is a clinical interest in novel actionable tools to help determine which CD38-targeting antibody is more suitable for each individual patient.



	Daratumumab	Isatuximab
Antibody-dependent cellular cytotoxicity (ADCC)	++	++
Antibody-dependent cellular phagocytosis (ADPC)	+++	$CD38^{hi}$ Only
Complement-dependent cytotoxicity (CDC)	+++	+
CD38 activity inhibition	+	+++
Apoptosis induced directly by Ab or by Ab cross-linking	By cross-linking only	Both
Regulation of CD38 expression	Vesicle secretion containing CD38	CD38 internalization
Immunomodulation	++	+++

Figure 1. Direct and Indirect Mechanisms of Action of mAbs targeting CD38

MoA: Mechanism of action

MDSC: Myeloid-derived suppressor cells

Aim

To predict the differential response to Dara and Isa antibodies in MM patients using the Patient Micro Avatar platform.

Methods

OncoPrecision has developed a technology named Patient Micro Avatars (PMAs) (Figure 2). This platform mimics the tumor microenvironment and promotes the survival of Patient-Derived Cells (PDCs), allowing the ex vivo testing of myeloma treatments (Marin C et al., Blood (2023) 142 (Supplement 1): 5033). Importantly, PMAs not only enable the evaluation of the direct cytotoxic activity of Dara and Isa, but to also assess the contribution of autologous effectors cells in triggering Antibody-Dependent Cellular Cytotoxicity (ADCC). We used PMAs to investigate the differential responses of Isa and Dara in a cohort of 25 MM patients (newly diagnosed and relapsed) from 6 healthcare centers in Argentina.

PMAs were treated with Dara and Isa and subsequently, the pathological population was analyzed by high-throughput automated flow cytometry using specific markers, and the percentage of survival was determined. For the interpretation and classification of response patterns to each treatment, a proprietary machine learning algorithm was used.

OncoPrecision's Technology: Patient Micro Avatars (PMAs)

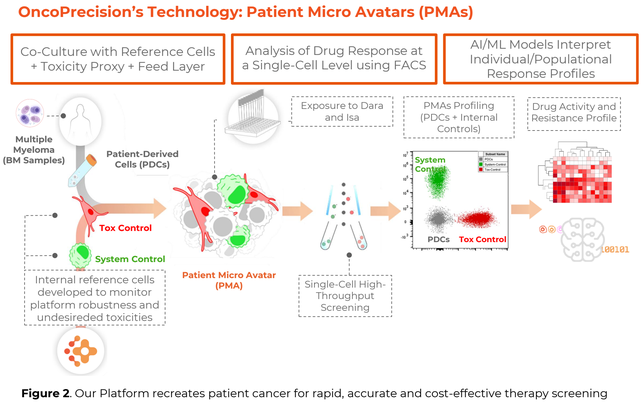
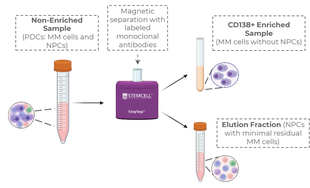


Figure 2. Our Platform recreates patient cancer for rapid, accurate and cost-effective therapy screening

Results

Positive Selection: isolating CD138+ MM cells



Ex-vivo Response to Daratumumab (AUC Heatmap)

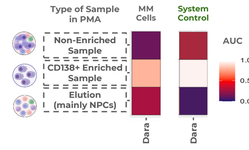


Figure 3. Our PMAs reveal the **essential role of Non-Plasma Cells** in predicting ex vivo response to anti-CD38 monoclonal antibodies in MM.
The response to Dara in CD38-positive cells varies depending on the percentage of NPCs present in the PMAs. MM cells and System Control cells (MM cell line that serves as an internal quality control) within PMAs from a CD138+ enriched sample, with a minimal residual NPC compartment, exhibit a lower response to Dara compared to those in a non-enriched sample containing both pathological cells and NPCs. Interestingly, when testing the eluted fraction (predominantly NPCs) in PMAs, we observed a strong effect on the System Control, underscoring the key role this population (NPCs) plays in antibody response.

Ex Vivo Response to Anti-CD38 Antibodies (AUC-Heatmap)

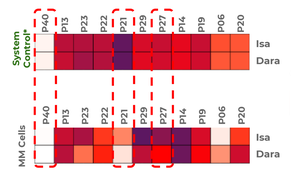


Table 1. Proportion of NPCs

Patient ID	NPCs proportion in BM samples (%)
P40	61
P13	47
P23	41
P22	41
P21	69
P29	82
P27	67
P14	50
P19	87
P06	40
P20	31

Figure 4. Comparison of anti-CD38 activity in our Platform: **Daratumumab vs. Isatuximab**.
Our Platform allows us to infer the proficiency of NPCs based on the differential responses observed in the System Control. Similar immune proficiencies in NPCs from different patients lead to differential responses against myeloma cells (MM cells)(e.g., Patient #22 vs. Patient #27). Highly proficient immune cells in the NPC compartment do not necessarily exhibit activity against the patient's myeloma cells (e.g., Patient #21). Non-functional NPCs fail to trigger a response to both Daratumumab and Isatuximab in System Control and MM cells (e.g., Patient #40). Moreover, we found no relationship between the proportion of NPCs in the sample and drug response (Table 1).

Comparison of Ex Vivo Response: Daratumumab vs Isatuximab

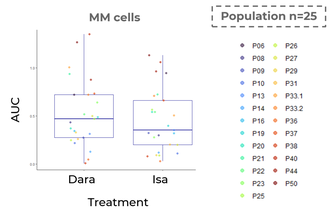


Figure 5. Proprietary Machine Learning algorithms analyzed the anti-CD38 antibody response in a cohort of 25 MM patients (newly diagnosed and refractory/relapsed).
Our PMAs, allowed us to compare the responses to both antibodies in the same patients, and the results showed a significant difference (p-value < 0.05), indicating that Isatuximab has a stronger effect than Daratumumab.

Summary

Our findings revealed a statistically significant difference between the responses to both mAbs ($p<0.05$), indicating that Isa has a more potent effect than Dara. Furthermore, our data suggests that while the abundance and proficiency of autologous effector cells are critical for achieving a full response to CD38 antibodies, the most notable differences in responses to Dara and Isa are largely determined by the intrinsic features of the MM cells from the different patients. This conclusion is supported by the observation that effector cells from these patients trigger similar ADCC in the System Control MM cell line, which serves as an internal quality control.

Discussion

The results of this study highlight the potential of PMAs to comprehensively evaluate the performance of therapeutic antibodies, including those designed for the same target, in patient-relevant contexts. Unlocking such translational insights may serve as a powerful tool with broad implications across the discovery and development of antibody-based therapies. Moreover, our investigation of the responses to Dara vs Isa indicates that these therapeutic antibodies are not always interchangeable, and their side-by-side evaluation merits further clinical investigation.

References

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