The anti-kappa monoclonal antibody MDX-1097 cooperates with Lenalidomide to enhance antibody-dependent cell cytotoxicity of multiple myeloma cells

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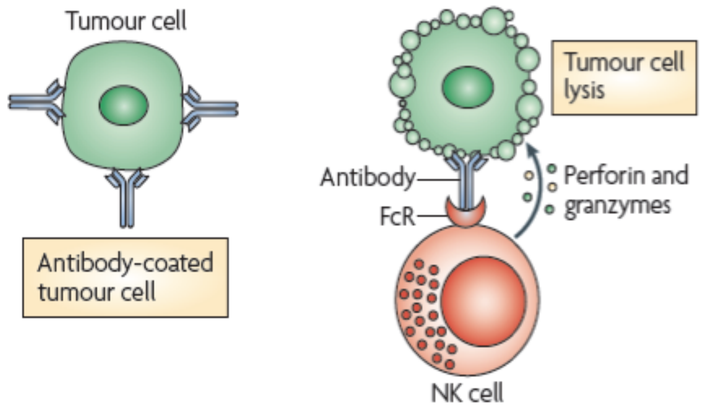
Introduction

- **Multiple Myeloma (MM)** is a malignancy of clonal plasma cells in the bone marrow[1]. Despite recent advances in the treatment and management of MM, the majority of patients will ultimately relapse and die from their disease within 3-5 years. In this context novel therapeutic approaches, including the use of antibody-based therapies, are being investigated to further improve the treatment of MM.
- **MDX-1097** is a chimeric monoclonal antibody currently being assessed as a single agent in a Phase 2 clinical trial for the treatment of kappa light-chain restricted (κ-type) MM. MDX-1097 binds to **kappa myeloma antigen (KMA)**, a tumor-specific membrane-associated protein expressed on malignant plasma cells in patients with κ-type MM. MDX-1097 exerts its anti-tumour effects via multiple mechanisms including antibody-dependent cell cytotoxicity (ADCC) in the presence of immune effector cells such as Natural Killer (NK) cells[2].
- **Lenalidomide** is an immunomodulatory drug currently used to treat MM. Lenalidomide exhibits both and indirect anti-tumor mechanisms. One such indirect anti-tumor mechanism mediated by Lenalidomide is through enhancment of NK-dependent cellular cytotoxicity[3].
- **Given that both MDX-1097 and Lenalidomide utilize immune effector cells such as NK cells as part of their anti-tumor reperitoire, we examined whether MDX-1097-bound MM cells would more effectively use Lenalidomide-treated peripheral blood (PB) immune effector cells to enhance MM cell death *in vitro*.**

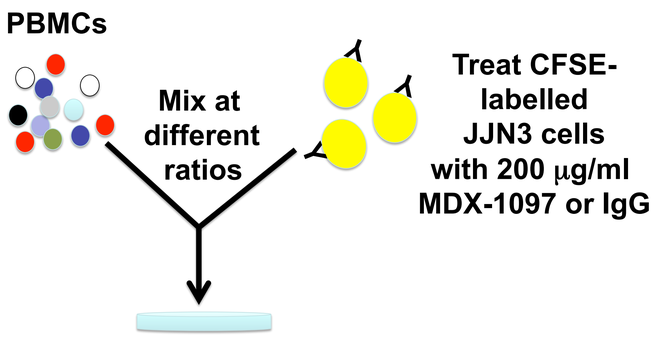
Antibody-Dependent Cell Cytotoxicity (ADCC)



Fc receptor (FcR)-expressing immune effector cells bind to the Fc portion of the tumour-bound antibody, which triggers the release of enzymes from effector cells resulting in tumor cell death.

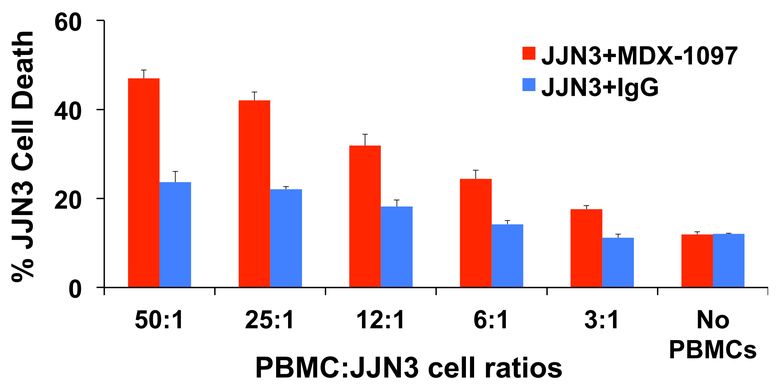
From Weiner et al (2010) *Nat Rev Immunol;* 10; 317-327

Schematic for FACS-based ADCC Assay



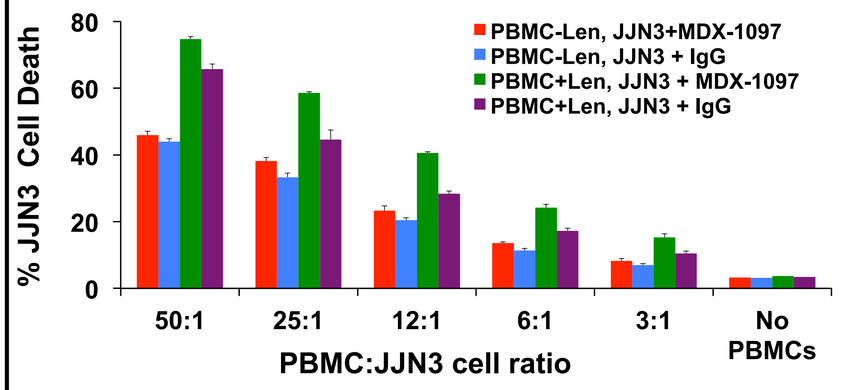
Incubate for 12 hours then add 7-AAD
Detect dead JJN3 cells (CFSE+/7-AAD+) by FACS

Figure 1: MDX-1097 enhances PB immune effector cell-mediated cell death of JJN3 cells



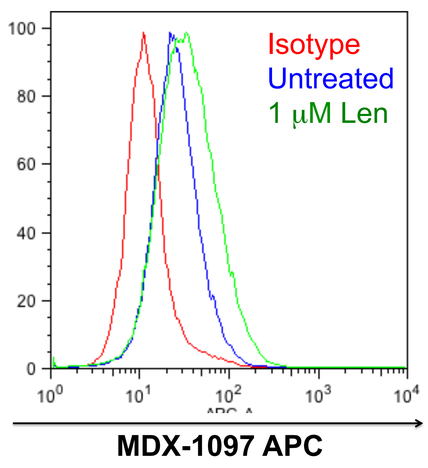
Observations: These results demonstrate that MDX-1097 coated MM cells are more susceptible to immune effector-mediated cell death compared to IgG-treated MM cells

Figure 2: Lenalidomide treated PBMCs increase MDX-1097-dependent JJN3 cell death

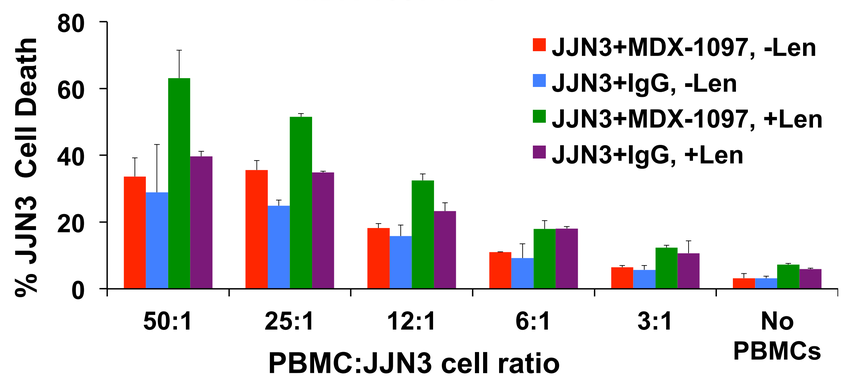


Observations: PBMCs were treated with 1 μM Lenalidomide (+Len) or vehicle (-Len) for 72 hours prior to ADCC. MDX-1097 bound MM cells more effectively utilizes Len-treated PBMCs to increase MM cell death compared to controls.

Figure 3: Lenalidomide enhances KMA expression on JJN3 cells, and increases PB immune effector cell-induced MDX-1097 dependent JJN3 cell killing

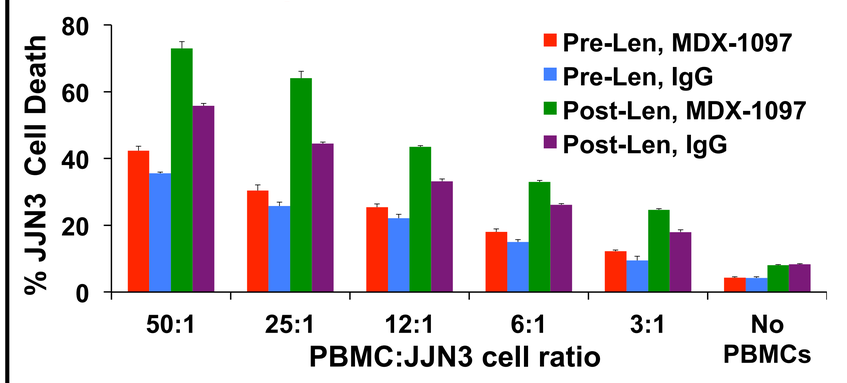


KMA expression on JJN3 cells



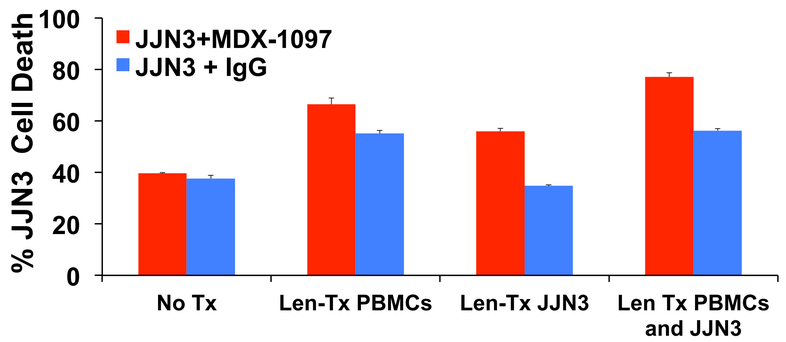
Observations: Treatment of JJN3 cells with 1 μM Len enhances KMA expression. This likely increases the number of binding sites for MDX-1097, leading to enhanced PB immune effector cell-mediated ADCC compared to untreated JJN3 cells.

Figure 4: PBMCs from Lenalidomide-treated MM patients induce higher levels of MDX-1097 dependent cell death.



Observations: PBMCs isolated from the same patient prior to and after Len treatment were incubated with MDX-1097 bound MM cells in an ADCC assay. As in Figure 2, MDX-1097 bound MM cells more effectively utilize the *in vivo* Len-treated PB immune effector cells s to enhance cell death of MM cells *in vitro*.

Figure 5: Lenalidomide-treated PBMCs are most effective against MDX-1097 bound, Lenaldomide-treated JJN3 cells



Observations: Vehicle or Len treated PBMCs and JJN3 cells were incubated together in various combinations at a fixed 50:1 PBMC:JJN3 ratio. The increased KMA levels on Len-treated JJN3 cells resulted in more MDX-1097 binding, which in turn enhanced MM cell death in the presence of Len-treated PBMCs.

Conclusions

- MDX-1097, when bound to MM cells, utilizes *in vitro* or *in vivo* Lenalidomide treated PB immune effector cells more effectively kill MM cells *in vitro*.
- Lenalidomide sensitises MM cells to PB immune effector cell mediated in part by enhancing KMA expression on MM cells, leading to more binding sites for MDX-1097.
- When MDX-1097 bound, Lenalidomide-treated MM cells, combined with Lenalidomide treated PBMCs, results in a higher level of MM cell death compared to untreated or singly-treated cell populations.
- **These results provide a rationale for the clinical evaluation of MDX-1097 in combination with Lenalidomide for the treatment of multiple myeloma**.

Acknowledgements

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References

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