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

AR Cuddihy[1], T Khong[1], R Dunn[2], P Asvadi[2] and A Spencer[1]

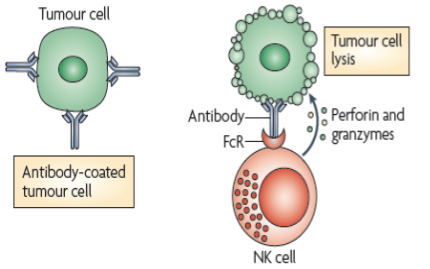
1. Myeloma Research Group, Division of Blood Cancers, Australian Centre for Blood Diseases, Monash University, and The Alfred Hospital, Melbourne, Ausralia and 2. Immune System Therapeutics, Sydney, Australia

ACBD Australian Centre for Blood Diseases | TheAlfred Malignant Haematology & Stem Cell Transplantation Service | MONASH University Medicine, Nursing and Health Sciences | Immune System Therapeutics Ltd

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** and **Pomalidomide** are immunomodulatory drugs (IMiDs) used to treat MM. These IMiDs exhibit both direct and indirect anti-tumor mechanisms. One such indirect anti-tumor mechanism mediated by IMiDs is enhancement of NK cell mediated 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*.**

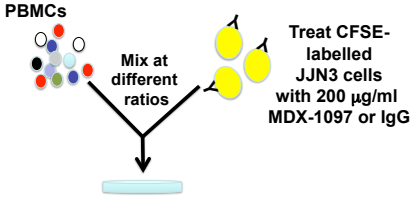
Antibody-Dependent Cell Cytotoxicity (ADCC)



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.

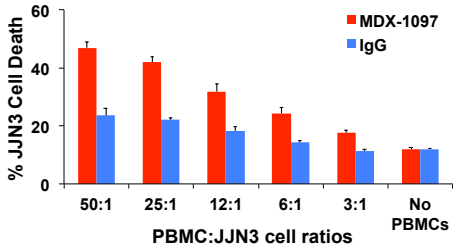
From Weiner et al (2010) *Nat Rev Immunol;* 10; 317-327

FACS-based ADCC Assay



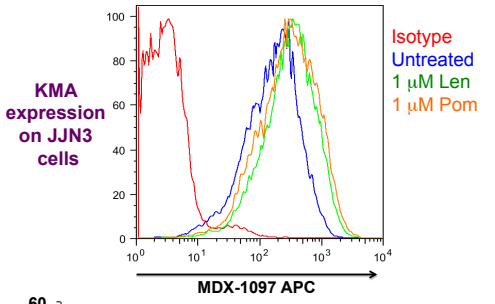
Incubate for 12 hours then add 7-AAD
Detect dead JJN3 cells (CFSE+/7-AAD+) by FACS

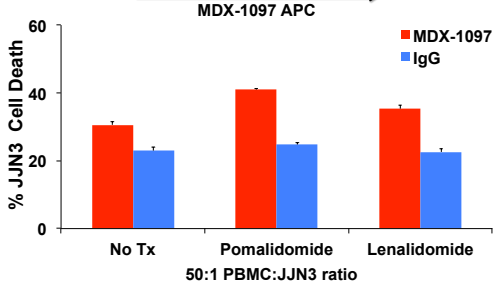
Figure 1: MDX-1097 enhances PB immune effector cell-mediated cell death of JJN3 cells



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 3: IMiDs enhance KMA expression on JJN3 cells, and increase PB immune effector cell-induced MDX-1097 dependent JJN3 cell killing



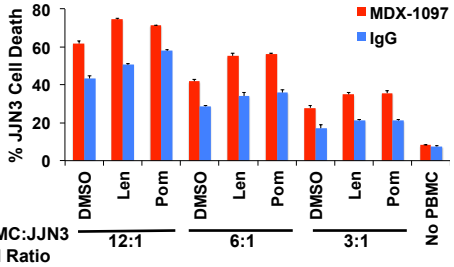


Observations: Treatment of JJN3 cells with 1 µM Pom or Len enhances KMA expression. This likely increases the number of binding sites for MDX-1097, leading to enhanced PB immune effector cell-mediated ADCC compared to untreated JJN3 cells.

Conclusions

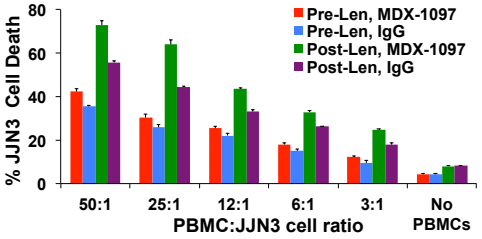
- Exposure of PBMCs to IMiDs, both *in vitro* and *in vivo*, enhances MDX-1097 mediated JJN3 cell death.
- Pre-treatment of JJN3 cells with IMiDs increases KMA expression, leading to more binding sites for MDX-1097. This correlates with an increase in PB effector cell mediated JJN3 cell death,
- IMiD-treated MM cells combined with IMiD-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 IMiDs for the treatment of multiple myeloma.**

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



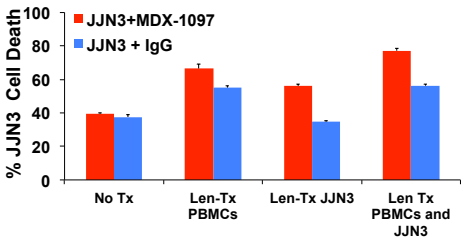
Observations: Normal donor PBMCs were treated with 1 µM Lenalidomide (Len), 1 mM Pomalidomide (Pom) or vehicle (DMSO) for 72 hours prior to ADCC. IMiD treated PBMCs are more effective at inducing MDX-1097 mediated toxicity against JJN3 cells.

Figure 4: PBMCs from IMiD-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, Lenalidomide-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.

Acknowledgements

We thank Celgene Corporation for providing Lenalidomide and Pomalidomide, and Immune System Therapeutics for providing MDX-1097 and research support.

References

1. Raab, MS et al ***Lancet* (2009); 374: 324–39**
2. Asvadi, P. et al ***Submitted***
3. Richardson, P et al ***Core Evid***. (2010);4:215-45