The anti-KMA monoclonal antibody MDX-1097 cooperates with IMiDs and HDACi 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 die within 3-5 years. Several 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 (mAb) 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].

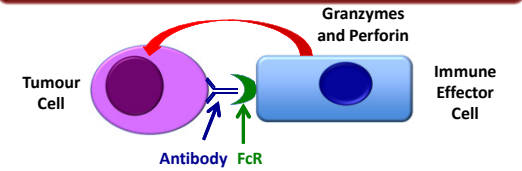
Lenalidomide and **Pomalidomide** are both immunomodulatory drugs (IMiDs) used to treat MM. These IMiDs exhibit both direct and indirect anti-tumor mechanisms. One such indirect anti-tumor mechanism mediated by IMiDs is through enhancement of NK-dependent cellular cytotoxicity[3]. IMiD-treated immune effector cells have been shown to potentiate ADCC-mediated responses to hematological tumor cells in the presence of other therapeutic mAbs.

Histone deacetylase inhibitors (HDACi) are a class of drugs that have demonstrated antiproliferative and pro-apoptotic activities against both solid and hematological cancers[4]. A number of HDACi are currently being clinically assessed for the treatment and management of MM[5]. More recently, HDACi was shown to cooperate with therapeutic mAbs to more effectively kill tumor cells[6].

Objectives

- To investigate whether IMiD treated PBMCs induce more ADCC of MDX-1097-bound MM cells compared to untreated PBMCs.
- To examine whether MM cells treated with IMiDs and HDACi are more sensitive to MDX-1097-induced ADCC in the presence of PBMCs.

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 such as granzymes and perforin from effector cells causing tumor cell lysis and resulting in tumor cell death.

FACS-based ADCC Assay

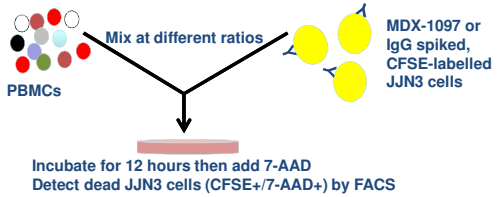
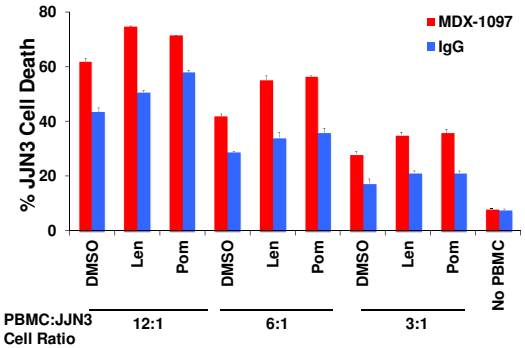
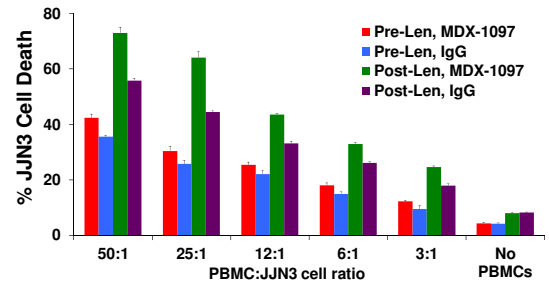


Figure 1: *In vitro* IMiD-treated PBMCs increase MDX-1097 dependent MM cell death



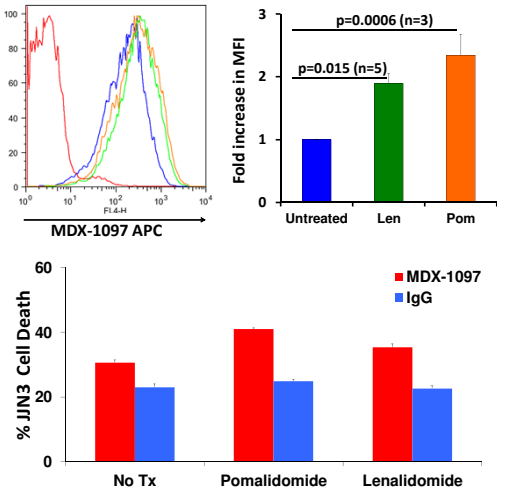
Observations: PBMCs were treated with 1 μM Lenalidomide (Len), 1 μM Pomalidomide (Pom) or vehicle (DMSO) for 72 hours prior to ADCC. MDX-1097 bound MM cells more effectively utilize IMiD-treated PBMCs to increase MM cell death compared to controls.

Figure 2: PBMCs from Lenalidomide-treated MM patients induce higher levels of MDX-1097 dependent MM cell death



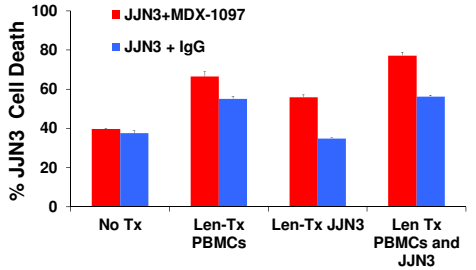
Observations: PBMCs isolated from the same patient prior to and after Len treatment (10 mg/day) were mixed with MDX-1097 or IgG spiked MM cells. MDX-1097-bound MM cells more effectively utilize the *in vivo* Len-treated PB immune effector cells to enhance cell death of MM cells *in vitro*.

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



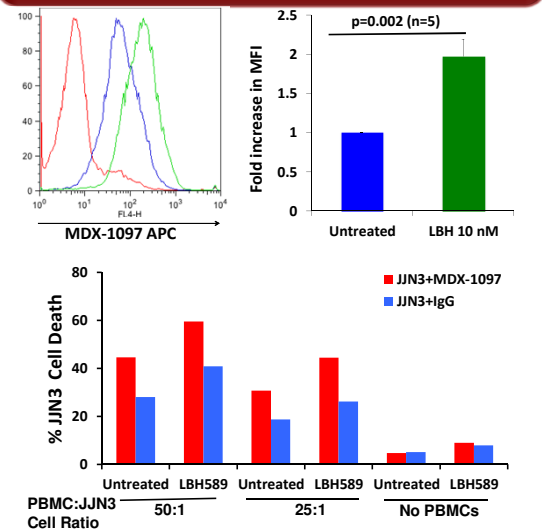
Observations: Treatment of JJN3 cells with 1 μM Lenalidomide (Len) or 1 μM Pomalidomide (Pom) increases KMA expression. Blue histogram indicates isotype control. IMiD treatment also sensitises cells to enhanced PB immune effector cell-mediated ADCC in the presence of MDX-1097 compared to untreated JJN3 cells. Data shown is for a 50 to 1 PBMC:JJN3 cell ratio.

Figure 4: Lenalidomide-treated PBMCs are most effective against MDX-1097 bound, Lenalidomide-treated MM 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.

Figure 5: The HDACi LBH589 enhances KMA expression on MM cells and increases immune effector cell-induced MDX-1097 dependent MM cell killing



Observations: Treatment of JJN3 cells with 10 nM LBH589 increases KMA expression. Blue histogram indicates isotype control. LBH589 treatment also sensitises JJN3 cells to enhanced PB immune effector cell-mediated ADCC in the presence of MDX-1097 compared to untreated JJN3 cells.

Summary

- MDX-1097, when bound to MM cells, utilizes *in vitro* or *in vivo* IMiD treated PB immune effector cells to more effectively kill MM cells *in vitro*.
- Both IMiDs and HDACi sensitise MM cells to PB immune effector cell mediated killing, in part by enhancing KMA expression on MM cells, leading to more binding sites for MDX-1097 and thus providing more FcR binding sites.
- MDX-1097 bound, 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 and HDACi for the treatment of multiple myeloma.

References

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