MDX-1097 binds Kappa Myeloma Cells Specifically and Its Anti-tumour Activity is Mediated by Multiple Effector Cells

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Introduction

MDX-1097 is a monoclonal antibody currently in clinical trial to evaluate its safety and efficacy in the treatment of kappa light chain overexpressed multiple myeloma (kMM) patients with stable measurable disease. MDX-1097 binds a conformational epitope on soluble free light chain (kFLC) and the kappa myeloma antigen (KMA) which consists of membrane bound kappa light chain restricted multiple myeloma (kMM) patients with stable measurable disease. MDX-1097 binds to bone marrow cells derived from the bone marrow (BM) of kMM patients, cells derived from bone marrow samples from patients with kappa plasma cell dyscrasia and on KMM cell lines.

Preclinical studies using the murine version of the monoclonal antibody, mKap, demonstrated that the antibody could induce growth inhibition and apoptosis of KMM cell lines. In addition, mKap was able to inhibit tumor growth in a SCID xenograft model of myeloma.

Data presented here demonstrates the presence of KMA and the co-expression of the B cell surface antigens CD138, CD38 and CD11b on cells derived from the bone marrow (BM) of kMM patients. Immunohistochemistry staining shows specific binding of MDX-1097 to plasma cells in bone marrow sections taken from samples with kappa plasma cell dyscrasia and no binding to normal BM cells. CD138+ cellscontaining a range of KFLC concentrations is also presented. Finally, the functional aspects of MDX-1097 binding to KMM cells in ex vivo models were assessed.

MDX-1097 mediates antibody dependent cellular cytotoxicity (ADCC) in the presence of activated effector cells and antibody dependent cellular phagocytosis (ADCP) in the presence of macrophages isolated from normal human bone marrow.

MDX-1097 binds to bone marrow cells derived from kappa multiple myeloma patients

Conclusions

- MDX-1097 binds specifically to KMA, a membrane-associated antigen composed of free kappa light chains present on cells derived from kappa myeloma patients. Unlike the majority of the BM samples analyzed, KMA was present on cells in the CD38+CD138+ phenotype. It has been suggested that the CD45+CD11b+ phenotype in MM is associated with a higher proliferative index and more aggressive disease. It has been suggested that the CD45+CD11b+ phenotype. KMA was also present on a subset of CD45+CD138+ cells in the bone marrow of patients with kappa plasma cell dyscrasia and did not bind to cells from patients with lambda plasma cell dyscrasia. No target binding was observed in the normal human tissue panel.

- The ability of MDX-1097 to bind myeloma cells (KMA) in the presence of human serum indicated that the antibody is able to engage membrane associated antigen (KMA) in the presence of soluble light chain. One explanation for this observation is that the antibody has a low affinity (2x10·9 M−1) for the soluble light chain. This antibody likely has a transitory binding of the membrane associated antigen due to antibody effector function.

- In vitro experiments showed that MDX-1097 was able to mediate ADCD and this is probably one of the mechanisms that confer anti-tumour activity in vivo.

- Enhanced macrophage phagocytosis of MDX-1097 coated myeloma cells was demonstrated in vitro. This mechanism of action is likely to occur in vivo as macrophages are present in the haematopoetic islands within the bone marrow.

References