MDX-1097 Binds Specifically to Kappa Myeloma Cells and Anti-Tumour Activity Is Mediated by Multiple Effector Cells.

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Previous studies have described a murine monoclonal antibody, mKap, that specifically recognizes a cell surface antigen expressed on kappa myeloma cells and not on normal lymphoid cells. This antigen has been identified and designated kappa myeloma antigen (KMA). KMA consists of free kappa light chains (kFLC) not associated with heavy chain and is present on plasma cells isolated from kappa myeloma (MMk) patient bone marrow aspirates, kappa myeloma cell lines and kappa macroglobulinemia. In vitro data demonstrated that mKap was able to inhibit cell growth and induce apoptosis in myeloma cell lines. In addition, preclinical studies demonstrated that mKap was well tolerated and showed significant efficacy in a SCID xenograft model of MM.

MDX-1097 is a chimeric version of mKap that is currently in development for the treatment of kappa restricted multiple myeloma. The antibody retains the binding affinity and specificity of mKap. Specific binding of MDX-1097 to malignant plasma cells isolated from MMk patient bone marrow aspirates has recently been demonstrated by flow cytometry. In addition a human tissue cross-reactivity study was performed using immunohistochemistry to assess the potential binding of MDX-1097-FITC to cryosections taken from a human tissue panel of three normal donors. The results demonstrated that MDX-1097 bound to bone marrow plasma cells from two patients with kappa cell dyscrasia but did not bind to normal human tissue samples or to plasma cells from a patient with lambda plasmacytoma. The ability of serum kFLC to inhibit MDX-1097 binding to the myeloma cell line, JN3, was assessed by flow cytometry using serum derived from 32 MMk patients. The results indicated that MDX-1097 at a concentration of 100µg/mL (equivalent to an estimated serum concentration of 5mg/kg dose) is capable of binding to myeloma cells in the presence of 0-250µg/mL of serum kFLC. In vitro functional studies have demonstrated that MDX-1097 engages Fc receptor bearing effector cells and induces antibody dependent cellular cytotoxicity (ADCC) in kappa myeloma cell lines in the presence of healthy donor peripheral blood mononuclear cells. Further investigations have verified that purified natural killer cells (NK) play a major role in MDX-1097 anti-tumour activity. Importantly, recent studies have demonstrated that antibody dependent cellular phagocytosis by macrophages contributes to the anti-tumour activity of several therapeutic monoclonal antibodies. Preliminary data indicates that MDX-1097 may be capable of inducing enhanced uptake by macrophages.

In conclusion MDX-1097 showed specific binding to KMA on myeloma cells isolated from patient's bone marrow samples and antibody binding is observed in the presence of kFLC in patient serum. In addition MDX-1097 anti-tumour activity is probably mediated by multiple Fc receptor bearing effector cells.


Footnotes

* Asterisk with author names denotes non-ASH members.