**Rituximab Induced Antibody Dependent Cell Mediated Cytotoxicity (ADCC) Is Enhanced By Thalidomide And Its Analogue Revimid.**

Toshiaki Hayashi, MD PhD 1,2*, Kenneth C Anderson, MD 1,2 and Steven P Treon, MD MA PhD 1,2. 1Medical Oncology, Dana Farber Cancer Institute, Boston, MA, United States, 02115 and 2Department of Medicine, Harvard Medical School, Boston, MA, United States, 02115.

Recent studies suggest that ADCC plays a central role for Rituximab induced tumor cell killing in vivo, and that use of cytokines which facilitate ADCC function appear to enhance clinical activity of Rituximab in low grade NHL. Recently, we demonstrated that Thalidomide and its analogue, Revimid (ImiD1) which is currently in Phase II trials in multiple myeloma (MM), enhanced PBMC mediated lysis of MM cells (Blood.2001; 98:210-6). In these studies, we examined the effect of Thalidomide and Revimid on Rituximab mediated ADCC activity of CD20+ ARH-77 cells. Normal donor PBMC were incubated with and without Thalidomide (5 uM) and Revimid (5 uM) for 72 hours prior to co-culture with 51Cr labeled ARH-77 cells in the presence or absence of Rituximab or isotype control antibody (10 ug/ml) for 6 hrs. These studies demonstrated that Rituximab mediated ADCC killing of ARH-77 cells was significantly enhanced by Thalidomide (27.1% vs. 13.2%; p= 0.02) and Revimid (37.3% vs. 13.2%; p= 0.02) treated PBMC versus untreated control PBMC. To evaluate whether changes in Fc receptor expression of PBMC was responsible for enhanced ADCC by Thalidomide and Revimid treated PBMC, changes in CD16 (FcgammaRIIIa) and CD64 (FcgammaRIa) expression on effector cell populations were evaluated following treatment with Thalidomide and Revimid; however, no changes in cell surface expression for these receptors was observed. In conclusion, both Thalidomide and Revimid significantly enhance ADCC activity mediated by Rituximab. A clinical trial examining the combination of rituximab with these agents in Waldenstrom's macroglobulinemia (WM) is being planned.