

# Pomalidomide treatment enhances survival in myeloma patients via immune modulation

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## Description

Pomalidomide is an immune-modulatory drug, structurally related to thalidomide and lenalidomide. It is approved by the Food and Drug Administration (FDA) for the treatment of Multiple Myeloma (MM). These three immunomodulatory drugs are known to target cereblon, an E3 ubiquitin, and to increase the degradation of Ikaros family of Zinc Finger protein 1 and 3 (IKZF1/3) transcription factors. Downstream related-proteins, including Interferon Regulatory Factor-4 (IRF-4) and c-Myc are also downregulated by these immunomodulatory drugs. Their anti-tumor effects are directly cytotoxic to MM cells and may in part improve antimyeloma responses of Natural Killer (NK) and T-cells. The clinical responses and survival benefits of these immune-modulatory drugs might be due to their ability to blockade certain check-point inhibitory molecules on immune cells. In a randomized, open-label, international phase 3 trial with 559 relapsed/refractory MM patients were treated with Pomalidomide, Velcade, and Dexamethasone (PVD) or Velcade, and Dexamethasone (Vd).

PVD treated patients showed significantly improved progression-free survival compared to Vd treatment (median PFS of 11.2 months vs 7.1 months). Furthermore, PVD treatment was shown to be effective for patient's refractory to lenalidomide treatment. A recently published paper from this group is the first to study the in-depth effect of doublet therapy Vd or triplet therapy PVD on 33 immune subpopulations using the OP TIMISMM trial. 366 PBMC samples from 186 patients were analyzed for associations between improved outcome upon addition of pomalidomide and its impact on immune milieu.

Immunomodulatory agents can favorably impact NK cell composition, both in terms of total CD16+CD56+ cells and proliferating Ki67+ NK cells. While we found that the total number of CD56+ NK cells were lower in frequency following Vd treatment, this is not seen with PVD treatment. The higher expression of double-positive NKG2D/p46 on NK cells and lower expression of double-positive KIR molecules (CD158a/b) on NK T-cells were observed in both PVD- and Vd-treated patients. We observed positive association of PFS with NK cells expressing activation and KIR molecules after PVD treatment. At cycle 1, a higher number of NK cells expressing NKG2D alone was associated with improved PFS in

patients treated with PVD and this is not observed in Vd treated patients. In addition, among paired samples between screening and cycle 3, PFS in PVD treated patients was influenced in a favorable fashion with increased number of NK cells that are double-positive for NKG2D and p46. Moreover, we show that the decreased number of KIR-expressing (CD158a/b) NK cells by PVD treatment enhanced PFS. CD158b (KIR2DL2, KIR2DL3, KIR2DS2) are generally expressed on Natural Killer (NK) cells and a subset of T cells. They feature two immunoglobulin C2-type domains that belong to the KIR (Killer-cell Immunoglobulin-like Receptors) family of molecules. CD158b must interact with specific HLA-C antigens on a target cell (HLA-Cw1, HLA-Cw3, HLA-Cw7 alleles) whereupon this interaction will inhibit cytotoxicity and prevent target cell lysis and death. CD158a (KIR2DL1), another KIR molecule, participates in inhibitory activities of NK cells via HLA-C molecules. The interactions between KIR and MHC class I molecules are important in balancing the NK cell and T-cell homeostasis. The absence of such interactions may cause lower levels of activation and may increase the susceptibility to autoimmune diseases. If the expression of a predictive marker like CD158b is lower than median on NK T-cells at screening, PVD treated patients showed significantly better PFS (12 months). Patients whose NK cells express lower than median CD158b at cycle 3-day 8 following PVD treatment, exhibited enhanced PFS (by 6 months) compared to patients expressing higher than median CD158b. Finally, when patients double expression of CD158a and CD158b on NK cells were lower than median at cycle 1 day-8 following PVD treatment, they showed significantly improved PFS (18 months). These results show that PVD treatment increases PFS by reducing the expression of KIR molecules on NK cells in myeloma patients. This observation is not seen in myeloma patients treated with Vd only. NKG2D (Natural Killer Group-2D, CD314) is an activation surface marker and generally expressed on NK, gamma/delta T-cells, and CD8+ T-cells. The Prabhala study in frontiers in oncology explores the immunomodulation of NK, NKT, and B/T-cell subtypes in relapsed/refractory multiple myeloma patients undergoing treatment with pomalidomide, velcade, and dexamethasone, elucidating its association with enhanced progression-free survival. It interacts with HLA class I molecules, including MIC (MHC class I related) and RAET1 (Retinoic Acid Early Transcript 1)/ULBP (Unique-Long16-Binding Protein) expressed on the surface of stressed, malignant transformed, and infected cells. When the expression of a

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prognostic activation marker, like NKG2D on NK cells is higher than median, a significant association with enhanced PFS (by 14 months) following PVd treatment at cycle 1 day 8 for myeloma patients are seen. PVd treatment improved the PFS in myeloma patients by increasing the expression of activation makers on NK cells, an effect not seen in Vd treated patients. These results clearly indicate that pomalidomide can increase the expression of activation markers and down regulate the expression of KIR inhibitory molecules on NK cells to enhance the PFS in myeloma patients following the treatment. PVd treatment decreased the population of regulatory B cells (Breg), which could decrease IL-10 production, thus limiting regulatory T cell (Treg) expansion and enhancing immune function. PVd-treated patients did not have decreased populations of B1a and IRA B-cells unlike Vd-treated patients, indicating improved innate immunity. If myeloma patients have lower numbers of IRA-B-cells at screening, the addition of pomalidomide to Vd treatment may control inflammatory burden by enhancing innate immunity and increase patient survival by up to 21 months. Consistently, patients treated with PVd also expressed higher proportions of B1b cells compared to Vd patients. These observations lead us to hypothesize that a pomalidomide-containing regimen could confer enhanced immunity and thus a favorable safety profile with regards to decreased incidence of opportunistic infection. Indeed, immune cell-enhancements are seen in two newer agents, iberdomide and CC-92480. When B-cells from Systemic Lupus Erythematosus (SLE) patients are cultured in the presence or absence of iberdomide, the B-cells ability to produce auto antibodies was decreased by iberdomide. In vitro, iberdomide was able to stimulate T-cells, isolated from healthy donors, to produce IL-2 using

anti-CD3 stimulation, while IL-1-beta production by LPS was reduced. These results indicate that the attribute characteristics of SLE, including auto-antibody production, regulatory Tcell-dysfunction and inflammatory responses could be inhibited by iberdomide. Myeloma patients treated with PVd showed the involvement of four prognostic markers (OX-40+CD8, PD-1+CD4 and CD25+CD4) with survival. These results indicate that the addition of pomalidomide to Vd treatment may improve clinical response and patient's survival by increasing the expression of OX40 on CD8 T-cells; and by reducing the expression of PD-1on CD4+T-cells and the number of regulatory T-cells. It appears that addition of pomalidomide to Vd further increased the number of CD8+T-cells expressing OX-40, a co-stimulatory molecule, and this increase at cycle 3 day-8 is favorably associated with PFS by increasing patient's survival up to 10 months. On the other hand, the decreased number CD4+ cells expressing PD-1, a check-point inhibitory molecule, at cycle 3 day-8 following PVd treatment can enhance the overall anti-myeloma response, and subsequently PFS was improved by 14 months. Finally, downregulating the number of high CD25-expressing regulatory T-cells with PVd treatment at cycle 3 prolongs survival in patients by up to 1 year. These PFS improvements are not seen in Vd treated patients. In summary, the prognostic significance of immune markers by PFS was only observed in PVd treated patients. Thus, this study exhibits the importance of the immunomodulatory effects for therapeutic benefit by adding pomalidomide to Vd treatment.

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