Effect of IMiD Compounds on CD38 Expression on Multiple Myeloma Cells: MOR202, a Human CD38 Antibody in Combination with Pomalidomide

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Abstract

Background: MOR202 (MOR30087), a human CD38 antibody currently under evaluation in a phase II trial, mediates antibody-dependent cell-mediated cytotoxicity/phagocytosis (ADCC/ADCP) of multiple myeloma (MM) patient-derived cells with high potency (EC50 ~200 nM). IMiD compounds such as lenalidomide (LEN) or pomalidomide (POM), both approved in MM, were evaluated in vitro for their ability to modulate CD38 expression and enhance the cytotoxicity of MOR202.

Methods: CD38 expression +/- LEN and POM on MM cell lines was analyzed by flow cytometry. The antitumour activity of POM combined with MOR202 was evaluated in vitro; analyses included induction of direct cytotoxicity of MM cells and the activation of immune effector cells. On a functional level, the combinatorial effects of MOR202 with POM were assessed in ADCC assays. Different incubation schemes were used to separate the effect of POM on target and effector cells, as well as in the evaluation of the combined effects. The observed combination effects were analyzed for synergistic potential using the fractional product concept.

Results: POM and LEN mediated a substantial CD38 upregulation on MM cell lines. POM as a single agent showed activation of effector cells and with high potency (EC50 ~150 nM), cytotoxic effects on MM cell lines. Additionally, POM dose-dependently induced an up to 3.5-fold increase in CD38 expression on MM cell lines. POM-mediated cytotoxic effects were time-dependent, with the most pronounced effects after 72 h incubation. Combining MOR202 with POM led to a synergistic enhancement of cytotoxic activity. The synergy benefit ranged between 1.2–3.1-fold above theoretical additivity, depending on the cell line used, and was most prominent in case of strong CD38 upregulation.

Conclusions: Upregulation of CD38 was mediated by both LEN and POM and may represent a class effect of IMiD compounds. The cytotoxic activity of MOR202 on MM cells was enhanced by POM via multiple mechanisms: CD38 upregulation, activation of effector cells and direct cytotoxicity. These results provide a mechanistic rationale for the combination of MOR202 with IMiD compounds and warrant further clinical evaluation.

Conclusion

- CD38 upregulation on Multiple Myeloma cell lines may represent a class effect of IMiD compounds
- In combination therapy MOR202 activity on MM cell lines is significantly enhanced by pomalidomide via CD38 upregulation, effector cell activation and direct cytotoxicity