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Reduced RON Expression, DM1 resistance and MRP1 Upregulation Contributes to Resistance in Colon Cancer Cells against anti-RON Antibody-Drug Conjugate Zt/g4-DM1

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Zt/g4-DM1 is an antibody-drug conjugate that specifically delivers the potent cytotoxic payload maytansinoid (DM1) to RON receptor-positive cells. Despite its impressive preclinical efficacy in the initial stages of treatment in xenograft models, tumors-mediated by colon and PDAC cells were only partially inhibited by Zt/g4-DM1. In light of these findings, we wanted to investigate mechanisms involved in Zt/g4-DM1 resistance. As part of this work, we developed anti-RON Zt/g4-SMCC-DM1 resistant colon cancer HT29, HCT116, SW620 cells derived from tumors by continuous treatment at lower doses followed by incremental dose increases. Approximately 100-200 fold resistance to Zt/g4-DM1 developed in these cells and cross-resistance was observed other ADCs containing drugs with similar mechanism of action. Reduced RON expression, DM1 resistance and increased expression of the ABCC1 (MRP1) drug exporter compared to parental cells were primary mediators of resistance. Interestingly we found a small percentage of RON positive population in resistant cells, when isolated these RON⁺ clones from three cell lines exhibited stable drug refractoriness and altered intracellular trafficking as a unique underlying mechanism of resistance to Zt/g4-DM1. HT29R, HCT116R, SW620R cell lines showed resistance to unconjugated DM1 but not to other chemotherapeutic agents. Tumors derived from HT29R, HCT116R, SW620R grew in mice and were refractory to Zt/g4-DM1 compared with parental cells. Hence, acquired resistance to Zt/g4-DM1 was generated from cells derived from tumors by continuous drug exposure, and either increased ABCC1 protein or reduced RON expression and defective intracellular trafficking in case of RON⁺ resistant cells were primary mediators of resistance. These resistant cell models retained sensitivity to chemotherapeutics, suggesting that alternative therapies may help in overcoming acquired resistance.