Potential resistance mechanisms to T-DM1

• Low HER2 expression in cancer
• Masking of the HER2 epitope
• High p95HER2 expression
• Poor HER2-T-DM1 complex internalization
• Defective intracellular and endosomal trafficking of the HER2-T-DM1 complex
• Defective lysosomal degradation of T-DM1
• A high rate of HER2-T-DM1 recycling
• Drug efflux proteins

Availability of T-DM1 to cancer cells (e.g. pharmacokinetics, tumor vascularization)