

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

## ***Cancer cell with HER2 overexpression***

### **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

