Antibody-Drug Conjugates (ADCs) are engineered immunoconjugate drugs composed of 3 core components: (1) a monoclonal antibody and (2) one or more cytotoxic small molecules (known as warheads), attached via (3) a chemical linker. While ADCs have the potential to assist in the fight against cancer, clinical success has been hindered by a lack of understanding of the mechanisms driving ADC safety and efficacy, and difficulty in optimization of each subunit individually and within the context of the entire ADC. Here, we apply computational systems pharmacology approaches to study ADCs with pyrrolobenzodiazepine (PBD) as the cytotoxic drug entity, combining experimental data and mechanistic modeling to conduct simulations of ADCs in different experimental scenarios relevant to drug development. This computational model is calibrated and validated using in vitro experimental data provided by AstraZeneca for anti-HER2-PBD ADCs, which have antibodies targeting the HER2 antigen and carry PBD payloads with differing properties. We conduct sensitivity analyses to identify the most influential parameters in the system, and simulate different scenarios to understand the impact of key ADC characteristics, such as the Drug-to-Antibody Ratio (DAR), warhead potency, and linker design, and connect these to ADC efficacy and toxicity in vitro. This work is critical to understanding how ADC design translates to ADC function, enabling the comparison of novel treatment scenarios and the development of better oncology therapies.