Lectures

L10.02 DESIGN AND CLINICAL DEVELOPMENT OF ANTIBODY DRUG CONJUGATES

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Antibody drug conjugates (ADCs) represent a new and important therapeutic approach to treating human cancer as demonstrated by recent clinical results for brentuximab vedotin and trastuzumab emtansine. Trastuzumab emtansine is relatively unique among ADCs as the unconjugated antibody (trastuzumab) has anti-tumor activity. For the vast majority of other ADCs in development the antibody serves as a drug delivery vehicle and renders the linked cytotoxic drug inert until released. By functioning as a pro-drug and preferentially targeting antigen-expressing tumor cells over normal cells ADCs are intended to have a broader therapeutic index than conventionally administered cytotoxic chemotherapy. Although simplistic in concept ADCs present some unique challenges for drug developers including identification of appropriate target antigens and choice of linker-drug and antibody. Clinical development of ADCs shares many aspects typical of oncology drugs including clinical evaluation of the relationship between pharmacokinetics and efficacy and safety and the need for representative tumor tissue to evaluate potential predictive biomarkers and to understand mechanisms of acquired drug resistance at progression. Several ADCs in clinical development at Genentech which underscore these design and clinical evaluation principles will be discussed including ADCs directed against B-cell and solid tumor antigens.