Peripheral neuropathy with microtubule inhibitor containing antibody drug conjugates: Challenges and perspectives in translatability from nonclinical toxicology studies to the clinic

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Antibody drug conjugates (ADC) consist of potent cytotoxic drugs conjugated to antibodies via chemical linkers, which enables specific targeting of tumor cells while reducing systemic exposure to the cytotoxic drug to improve the therapeutic window of chemotherapy drugs. The valine citrulline monomethyl auristatin E (vcMMAE) ADC platform (conventional linker-drug conjugation) has shown promising clinical activity in a variety of cancers, but peripheral neuropathy (PN) has been observed in the clinic but not in nonclinical toxicology studies. We evaluated four possible hypotheses for the lack of translatability of PN in nonclinical toxicology studies with conventional vcMMAE ADCs: 1) exposure differences; 2) sensitivity of the animal model; 3) differences in how ADC properties manifest; and 4) susceptibility of clinical population. The result of this hypothesis-based approach identified several challenges with trying to model the PN observed in late stage oncology patients in our nonclinical toxicology studies with MTI containing ADCs due to a combination of factors related to all four hypotheses. However, it also enabled us to more systematically determine if a better in vivo animal model could be employed to improve translatability. While many data gaps still remain; increasing duration of exposure and incorporating an expanded neurohistopathology assessment of peripheral nerves in our nonclinical toxicology studies may enable us to reproduce the PN observed with conventional vcMMAE ADCs. The ultimate goal is to be able to have a model to screen the next generation MTI-ADCs for reduced incidence and severity of peripheral neuropathy.

Biography
Nicola Stagg has completed her PhD in Pharmacology and Toxicology from University of Arizona. She is a DABT Toxicologist in Drug Development with more than 8 years experience as a Nonclinical Toxicologist designing GLP and non-GLP toxicology studies, interpreting data, conducting mechanistic studies, submitting regulatory documents and presenting to regulatory agencies globally. She serves as a Lead Toxicologist for several antibody drug conjugate and large molecule oncology programs at Genentech. She has worked on over 20 different drug development programs. She is the author of 11 peer-reviewed journal articles, 2 patents and over 15 published abstracts.

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