Preclinical safety assessment of cytotoxic and biotechnology anticancer drugs complying with the regulatory, scientific and ethical aspects… what a challenge!

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The risk to develop cancer raises with age and this is why with an older population in developed countries, anti-cancer drugs are the first class of therapeutics to address unmet medical needs of industrialized world.
Before proceeding to the first use in human patients, the drug product needs to be tested in toxicity studies designed in agreement with indications reported in the international guidelines among which the leading document is now the ICH S9. The guideline applies to both small molecules and biopharmaceuticals but different scientific and ethical issues characterize the preclinical development of the two entities and this must be contemplated when tailoring the experimental plan. Typically, traditional cytotoxic compounds are tested on rat and dog causing a severe systemic toxicity in both animal models. This raises ethical concerns as it does the growing use of cynomolgus monkeys to investigate monoclonal antibodies which are the mostly used anti-cancer biopharmaceuticals.
Dog susceptibility to cytotoxic compounds can be a critical hindrance to the completion of a chronic toxicity study with anti-neoplastic products when doses exceeding the human ones are applied. In a preliminary study conducted in RTC, the minipig was used to find a suitable alternative and it showed a similar sensitivity to Doxorubicin when compared to man, but proved to be less vulnerable than dogs, thus allowing to explore wider ranges of doses. A long term study, exceeding the cumulative human equivalent dose was performed and this work confirms the relevance of the minipig as experimental model for toxicity studies with anti-neoplastic drugs, since all the animals given the number of planned treatment cycles showed some signs similar to humans and a greater ability to adapt to the effects of anticancers compared to dogs.
Biopharmaceuticals are often discovered in start-up companies and most biotech business are limited in size and budget and are keen to gather soon sound data about preclinical safety of their product. When a biotech company starts the preclinical development of a monoclonal antibody, use on Non-Human Primates (NHP) is often the only option due to lack of expression of relevant antigen in conventional toxicology species. Cynomolgus monkey strains are the most commonly used NHP, but, due to their size, a relevant amount of costly compound is necessary and this usually implies significant delays in the project progression.
Our recent experience of development of a monoclonal antibody in the common marmoset, confirmed the suitability of this model which is widely accepted by international regulatory authorities in alternative to the more costing and product-consuming macaque.
In this presentation the challenges of conducting preclinical safety assessment of anticancer drugs complying with the regulatory, scientific, economical and ethical drives will be presented and discussed with the aid of some case studies.