Utilizing panels of patient derived xenografts to aid the development of antibody drug conjugates

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ABSTRACT
Despite numerous endeavors in clinical trials there are few clinically approved Antibody Drug Conjugate (ADC) therapies. Here we comment on our recent publication demonstrating the power of using panels of patient-derived xenografts (PDX) prior to Phase 1, to assess the potential heterogeneity of response a clinical candidate may show across a population. Furthermore we discuss how the same approach has been used in an additional ADC program.

Abbreviations: ADC, Antibody drug conjugate; CDH6, Cadherin-6; CRO, contract research organization; DCR, Disease Control Rate; IHC, immunohistochemistry; L/P, Linker Payload; ORR, Overall Response Rate; PCT, PDX Clinical Trial; PDX, patient-derived xenograft; SoC, Standard of Care

The concept of antibody drug conjugates (ADCs) has been pursued for over two decades, and yet there are currently only four ADCs that are clinically approved in the USA, brentuximab vedotin, ado-trastuzumab emtansine and recently inotuzumab ozogamicin and the comeback of Gemtuzumab ozogamicin compared to over 60 ADC candidates in ongoing clinical trials. The strategies and challenges of first, second and third generation ADCs has been elegantly summarized in the recent Nature review by Beck et al. The most common pharmacology model used in selecting ADCs and projecting clinical activity are subcutaneous xenograft models. Challenges for translating preclinical efficacy data for ADCs to the clinic arise from several limitations of xenograft models. A program targeting another cell surface molecule with an ADC (ADC-X) was assessed in a PCT featuring 36 pancreatic tumor models (Fig. 1B). Only 20% responded to ADC-X, which, to screen for the most potent linker payloads (L/Ps) for an antibody drug conjugate; CDH6; HKT288; patient-derived xenograft; PCT

Results from these studies can be applied as a go/no go decision making step for the program, and inform patient selection strategies based on retrospective biomarker analysis.

The xenograft panel screen can also be informative at other stages of drug discovery. For example this approach can be used to screen for the most potent linker payloads (L/Ps) for an antibody. A program targeting another cell surface molecule with an ADC (ADC-X) was assessed in a PCT featuring 36 pancreatic xenografts models (Fig. 1B). Only 20% responded to ADC-X, which, being a lower than anticipated Disease Control Rate (DCR),
Further steps could be taken to make the PCT even more relevant to the current patient population, such as including models derived from patients post treatment, perhaps refractory or even resistant to Standard of Care (SoC) drugs for that indication or competitor therapies. Additionally, the accessibility of PDX models is increasing, and since the Gao 2015 paper numerous Contract Research Organizations (CROs) are offering "off the shelf" PDX models and PCT style 1×1×1 experiments, enabling pharma and biotech companies alike to test drug candidates in PDXs without the years of preparatory work of having to obtain, propagate, establish, classify and store these models. With these commercially available PDX resources, the point of entry to running PCT-style in vivo screens has been significantly lowered, providing a powerful pathway towards assessing response in heterogeneous populations and addressing the caveats of over-reliance on limited pharmacology models.

Disclosure of potential conflicts of interest

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Figure 1. The utility of Patient Derived Xenograft (PDX) Clinical Trials in Antibody drug conjugate (ADC) development. Fig 1A. Revised development process for all ADCs, to incorporate and PDX Clinical Trial (PCT) and thus assess efficacy in a panel of PDX models representing the intended patient population prior to Phase 1. PCT can also be utilized in optimizing Linker/Payload (L/P) step as indicated by arrow. Fig 1B. Efficacy of ADC-X, an ADC similar to HKT288 targeting a different cell surface antigen, in a Pancreatic PCT. Fig 1C. A subsequent Pancreatic PCT interrogating efficacy of ADC-Y, a modified version of ADC-X with altered L/P technology.