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COMMENTARY

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

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The concept of antibody drug conjugates (ADCs) has been pursued for over two decades[1], and yet there are currently only four ADCs that are clinically approved in the USA, brentuximab vedotin[2,3] ado-trastuzumab emtansine[4] and recently inotuzumab ozogamicin[5] and the comeback of Gemtuzumab ozogamicin[6] 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 2017.[7]

ADCs that have failed despite reaching their anticipated efficacious dose include among others, MLN2704.[8] In these cases, interrogation into the predictive power of the preclinical pharmacology models and how they were employed when investigating a target and selecting a lead is of uttermost importance to the field. 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 xenografts, but one common –yet preventable – pitfall is a reliance on a limited number of models. If a preclinical data package relies too heavily on a small number of models with a particular target expression pattern or payload sensitivity profile, an understanding of efficacy throughout a more heterogeneous population could be overestimated and lead to clinical trial failure.

We were cognizant of this fact throughout the Cadherin-6 (CDH6) targeting ADC program and opted for a different pre-clinical approach to understand potential efficacy in a clinical trial. In our recent manuscript[9] we detailed the use of a panel of Patient Derived Xenograft (PDX) models to gain understanding of our clinical lead, HKT288, prior to committing to clinical trials. We performed the 1 × 1 × 1 PDX Clinical Trial (PCT) design featured in Gao et al 2015[10] to test the efficacy of HKT288 across 30 unselected ovarian patient models which represented a heterogeneous spectrum of CDH6 expression. In this un-biased population there was a 40% response rate to a 5 mg/kg intravenous dose given every two weeks, and we demonstrated how response correlates well with target expression as defined by quantitative immunohistochemistry (IHC) or RNA expression analysis for CDH6. Furthermore, the response rate increased to 64% following a retrospective selection to include only the models with median IHC expression level of CDH6 and above in the analysis. Importantly, the range of expression levels noted in the PDX panel were relevant to the heterogeneity seen in the clinical population. These observations across a panel of PDX models provided a novel angle for the HKT288 preclinical pharmacology data package, which, contributing alongside a favorable preclinical safety data package, led to its progression into the clinic. Based on this experience, we believe an analogous approach would benefit the drug discovery process for ADCs more generally and would recommend profiling optimized leads with a dosing regimen enabling clinically-relevant exposures in a panel of PDX models representing the intended patient population (Fig. 1A).

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 PDX models (Fig. 1B). Only 20% responded to ADC-X, which, being a lower than anticipated Disease Control Rate (DCR),

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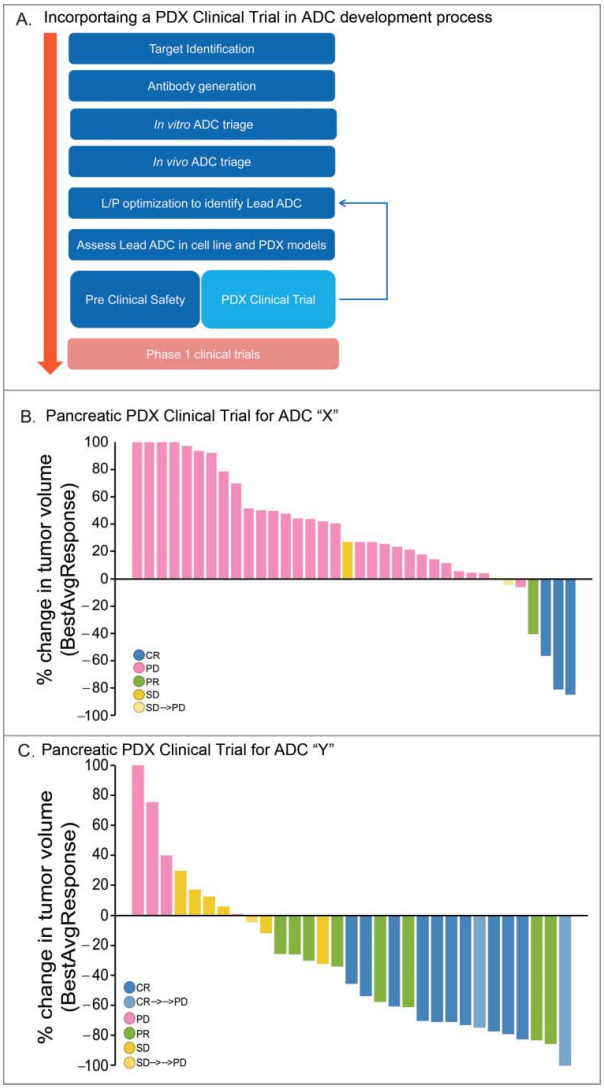

Figure 1. The utility of Patient Derived Xenograft (PDX) Clinical Trials in Antibody drug conjugate (ADC) development. Fig 1A. Revised development process for all ADCs, to incorporate and PDX Clinical Trial (PCT) and thus assess efficacy in a panel of PDX models representing the intended patient population 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.

supported a decision to halt the development of that particular configuration of antibody and L/P. However by altering the L/P technology for the antibody, the new ADC (ADC-Y) displayed vastly improved efficacy across a subsequent PCT using 31 pancreatic PDX models with a 65% ORR and a 90% DCR (Fig. 1C). These examples demonstrate that the PCT approach is versatile and can not only be informative for addressing translational aspects such as optimal patient selection strategies and understanding correlates of response(as in the case for HKT288), but also earlier in the drug discovery process, for instance during lead optimization (i.e. L/P selection).

Thus we propose that a PCT approach could become standard at various stages of the development of ADC therapies, providing a more stringent assessment of an agent as opposed to profiling a limited number of pharmacology models, which may not represent the clinical population. These studies enable confidence for further investment and clinical testing.

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

This research was funded by Novartis, Inc. and all authors were employees thereof at the time the study was performed. The authors declare no other competing financial interests.

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