charles river

Antibody Drug Conjugate Support Services

Services

- Discovery Support
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- Preclinical Study Design
- Bioanalytical Testing
- Immunology Endpoints
- Clinical Pathology
- Analytical Characterization and Testing

With the approvals of brentuximab vedotin (Adcetris®) and ado-trastuzumab emtansine (Kadcyla®), and the ongoing clinical and preclinical development of numerous similar molecules, antibody-drug conjugates (ADCs) are proving to be a powerful class of drugs for the treatment of cancer and other life-threatening diseases. Because of their complex nature, the development of ADCs requires a specialized approach that is tailored to address the potential safety issues of all components: the biotechnology-derived pharmaceutical (the antibody), the small molecule drug and the linker. As a world-leading CRO, Charles River has contributed to the development of many of the ADCs currently on the market or in clinical trials. Our comprehensive portfolio is uniquely suited to support the development of future therapies from early discovery to market and beyond.

Discovery Support

Charles River offers early research and proof-of-principle pharmacology studies in relevant animal models of human diseases to assist with efficacy evaluations. The scientific team at our oncology center of excellence has extensive experience running programs to validate pharmacokinetics (PK) and efficacy of ADCs *in vitro* and *in vivo*, collaborating with clients to select appropriate models and assays and design new models as needed. Our skilled toxicology and laboratory science teams can guide lead optimization, addressing critical factors such as *in vivo* stability, PK and toxicity in relevant rodent and nonrodent species.

Anatomic Pathology

We support ADC development with a variety of services, including GLP-compliant tissue cross-reactivity testing and immunohistochemistry-based biodistribution studies. For these types of studies, our staff can assist with protocol design and regulatory considerations, immunohistochemical staining method optimization, positive and negative control design, internal peer review, semi-quantitative assessment of immunostaining in context of histomorphologic and histopathologic changes, and full report preparation.

Considerations in Preclinical Study Design

The preclinical assessment of ADCs must include all three components – the antibody, the linker and the cytotoxic agent – and ideally be completed in the toxicology study. The approach can vary on a case-by-case basis; for example, if the whole complex is taken to or into the cancer cell, the testing approach may differ from one in which the linker cleaves on antibody binding. In some cases, an understanding of the function and toxicity of an individual component using available data may be sufficient. Regardless of whether information on the potential toxicity of either the antibody or the cytotoxic agent comes from within the same study as the ADC or from available data, the results of the ADC toxicology study should be interpreted in consideration of the known toxicities of each individual constituent. In addition, the potency of the cytotoxin also needs to be carefully managed, with the study design taking into consideration any myelosuppression and other class-specific effects. Finally, early discussion of the techniques used to support the animals while on study will ensure immediate action can be taken as necessary.

Laboratory Sciences

ADCs require extensive laboratory testing services to fully characterize the test material before dose administration, as well as to assess the PK/PD properties of the therapeutic. Prior to dosing, dose formation analysis via UV/Vis and HPLC to test both purity and concentration of the antibody-drug conjugate and the small molecule toxin must be conducted. Samples for bioanalysis, immunogenicity and a battery of other immunology endpoints should also be planned.

Charles River is experienced in developing and validating assays using a wide range of bioanalytical platforms to distinguish both total and conjugated therapeutic species in the determination of serum or plasma levels to evaluate exposure from early discovery through late phase clinical trials. Often, we develop and validate these alongside immunogenicity assays that will test for the formation of anti-therapeutic antibodies. Another valuable tool for the assessment of ADCs *ex vivo* is immunophenotyping and receptor occupancy assays via flow cytometry to characterize the pharmacodynamic effect of the therapeutic. Additional *in vitro* mechanistic assays may be required to understand and evaluate toxicities associated with the ADC.

Clinical Pathology

We offer in-depth assessment and interpretation of clinical pathology data for ADCs. It is important to assess the hematology, clinical biochemistry, coagulation, urinalysis, etc. to determine if there are any real or significant changes in the data, their relationship to the ADC and their potential adversity. Interpretation of clinical pathology data allows integration within life, histopathological and other type data (i.e., biomarkers), while linking to pathophysiological processes and organ functions. This assessment also takes into consideration species, study design, preanalytical and analytical factors, biological significance of the changes and their link to the pharmacological activity of ADCs.

Analytical Characterization and Testing

Our analytical services support the entire ADC product development cycle from initial product characterization, full IND-supporting reference standard characterization and method development/validation programs, all the way through to cGMP clinical product release and stability evaluation. ADC-tailored analytical services include drug-antibody ratio (DAR) determination, the development of methods for quantifying drug-conjugate components in support of PK and PD studies, analysis of free drug (payload) and naked carrier protein/antibody and site occupancy via mass spectrometry. Confirmation of secondary structure and aggregation are included in the higher order structural analysis and mapping of post translational modifications; disulfide bonds and glycosylation are also part of the characterization of the ADC. Forced degradation studies include degradant, impurity and isoform characterization. Along with formulation development, (including solubility and preformulation studies), we offer bridging studies and comparability programs.