Creating Clinical Target Validation Groups via Quality-Assured Transfer of Robust Clinical Pharmacodynamic (PD) Assays from the National Cancer Institute: Clinical Implementation of a HIF1α in Tumor Immunoassays

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Introduction

Early phase clinical trials of investigational agents benefit from laboratory assays that quantify the pharmacodynamic (PD) activity as terminal (T) PD effect and/or changes in biomarker (B) PD effect as a key endpoint in predicting clinical pharmacology and development of new agents and for identifying combinations of targeted agents, microenvironment, and biomarkers. Phase 0/1 clinical trials are valuable sources of tumor biopsies for evaluating PD, whereas Phase 0/1 trials are not. The National Cancer Institute’s Division of Cancer Treatment and Diagnosis (DCTD) develops and validates PD assays to obtain accurate information about drug effect on intended molecular targets in first-in-human clinical trials and inform clinical development decisions. The Pharmacodynamic Assays Development and Implementation Section (PDADS) and National Cancer Target Validation Laboratory (NCTVL) were established at SAIC-Frederick to develop and validate PD assays. Validating PD assays for clinical use involves validating analytical performance, demonstrating fitness-for-purpose for the clinical protocol, and confirming companion standard operating procedures (SOPs) for specimen handling and processing. Because clinical PD assays have strict assay performance that meet or exceed clinical diagnostic assays standards but key assay reagents are usually G-FD & rather than GMP-grade, reagent Quality Control is critical for preventing assay failures due to lot-to-lot variability. Prewritten clinical assays are transferred from the NCI to requesting sites in academia, the pharmaceutical industry, and other organizations via laboratory-based certification and training, centralized access to SOPs, assistance with assay transfer, and participation in the assay’s Quality Assurance Plan. The result is an assay user group that can reliably communicate assay issues, solve those issues, and implement required SOP changes while achieving consistent assay results across multiple sites over months to years of practical use.

Problem and Approach

Problem: There is no room for margin in the practical need for diagnostic activity and precision reagents and methods to deliver drug effects of targeted agents; these forces only arise after the targeted agents are shown to be clinically effective.

Approach: Achieve diagnostic-quality assays using materials and reagents from research support supplies that are suitable for the analysis of valuable and limited patient samples.

• Develop robust, accurate, and sensitive PD assays for preclinical and clinical use with collaboration between DCTD and NCTVL.

• Use proven, clinically available assay platforms such as immunoassays, circulating tumor cells, microarray, and bioanalyzer assays.

• Use assay instrumentation that has broad market availability so assays can be transferred to the community.

• Implement quality control programs borrowed from clinical laboratory medicine and GMP-manufacturing for key reagents.

• Meet rigorous performance standards to be considered clinically ready.

Conclusions

It is possible to develop robust assays to measure target engagement (T PD effect) as well as the downstream effect (B PD effect), and reliable responses (T PD effect) are more preferable for analysis of patient specimens, including their use as primary endpoints in Phase/Earlyphase (E) PD trials.

• Developing more stringent production and internal Quality Control (QC) specifications is crucial for accepting/rejecting new lots of critical reagents.

• Along with on-site training and SOP-based assays, other laboratories, QC of critical reagent supply chains is key to achieving consistent assay results over several years of clinical drug development.

• If you have a well-defined and effective QA plan, it is possible to conduct these PD assays with a network of users to achieve consistent results and quality across sites, assays, and times, using R&D-grade resource materials and critical reagents.