Editorial Commentary



# The use of research biopsies in oncology trials: challenges and controversies

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In a recent issue of *JAMA Oncology*, Dr. Christine Parseghian and colleagues reported on the rate of research biopsy reporting for registered clinical trials in the article entitled "Assessment of Reported Trial Characteristics, Rate of Publication, and Inclusion of Mandatory Biopsies of Research Biopsies in Clinical Trials in Oncology" (1). The authors undertook a systematic evaluation of oncologic investigation studies registered in ClinicalTrials.gov (CTG) over a 15-year period that conducted non-diagnostic solid tumor or lymph node biopsies. Any trials from January 1, 2000 to January 1, 2015 with the terms "biopsy", "biopsies", "tumor tissue", "tissue" or "cancer" were included in this analysis. This study found that "*despite ethical obligations to report research biopsies, only 50.8% of all trials that included a research biopsy-related end point in CTG reported on these biopsy-related results*", indicating that a significant improvement could be made in the clinical trial reporting of research biopsy results. Evaluation of factors correlating with research biopsy reporting led to identification of a trend in increased successful reporting over the period evaluated, categorization of the biopsies as mandatory as opposed to optional and having an objective for the biopsy collection. The authors stress the importance of transparency and accountability in the reporting of results obtained from research biopsies (1).

Successful pharmacodynamic studies resulting in reportable data require a multitude of elements (2-4). Usually this is in the realm of an early-phase clinical trial, as understanding the mechanism of action and selection of biomarkers—both predictive and prognostic—are critical to successful development of a drug, for example rucaparib and crizotinib (5,6). One of the most crucial elements to a successful clinical trial is the participation of the patient. In the initial stages of drug development, the research biopsy is necessary to answer a question about the drug rather than the patient, and so there is no direct benefit to the patient. The potential cost of time and biopsy risks are usually at the expense of the patient. A second consideration is the cost of the biopsy procedure; as research biopsies are not covered by insurance, the study site or sponsoring organization may have to cover the expense. Without significant financial support for, not just the biopsy, but the supporting infrastructure, including interventional radiology, laboratory equipment, and staff, pharmacodynamic correlatives in studies are not possible (7).

Even if the hurdles of patient participation and financial support are addressed, it takes the coordinated efforts of dedicated experts from a broad range of laboratory and medical disciplines to support the work necessary to generate critical knowledge from the effective analysis of research biopsies. Prior to clinical trial use, drugs and proposed biomarkers must be evaluated in parallel to guide the identification of informative biomarkers and the full optimization of robust analytical measurements. Beyond adequate biomarker assay development, the establishment of clinical readiness of the measurements is

of vital importance. Preclinical modeling of the assay must demonstrate endpoint quantitation with a performance and range suitable for the intended clinical use (8). The appropriate timing of biopsy collection in a clinically feasible time frame must be determined. Robust specimen collection, handling, and processing procedures must be developed to minimize preanalytical variables such as biopsy ischemia time. Adequately trained and available staff to perform critical specimen stabilization procedures in the clinical center and processing laboratory are also needed (9,10). The clinical trial protocol must include all relevant biomarker assay requirements including appropriate biopsy specimen collection parameters and timepoints as well as a thorough statistical plan including justification for the designated number of patients and biopsy specimens. Without these critical steps, the results may not be interpretable and therefore, unreportable (2-4).

In our experience, a fundamental barrier to successful reporting of pharmacodynamic endpoints from biopsies is the quality of the biopsy sample (4). Despite establishing stringent post-collection handling and processing procedures (11), an adequate specimen with viable tumor content is not always possible due to tumor heterogeneity. An analysis of four historical clinical trials conducted at the National Cancer Institute's (NCI) Developmental Therapeutics Clinic (DTC) revealed that only 74% of samples collected met the required quality control criteria for use in the intended assay (2,4). For trials in which two adequate biopsies (i.e., paired pre-dose and post-dose) from the same patient were required, this translated to approximately a 50% success rate. Many factors contributed to specimen inadequacy, but the overall central issue was insufficient viable tumor content. Critical to consider is that biopsies collected for evaluation of research endpoints often require higher tumor content than successful diagnostic biopsies for which the presence of even a small number of cells with specific morphological features and/or positive staining for one or more diagnostic biomarkers is often adequate. The NCI had convened national meetings with medical oncologists, diagnostic and interventional radiologists, and pathologists to review current practices at NCI and other cancer centers with the aim of identifying avenues to improve the quality of research biopsies. Major concerns of participants included a lack of recognition of the different requirements for research and diagnostic biopsy specimens, lack of communication between the oncology and radiology teams regarding the research biopsy specimen requirements and insufficient academic and financial recognition for the interventional radiologist's significant time investment required to support clinical trial research biopsy collections. Because of these discussions, several critical recommendations to improve cancer clinical trial research biopsy quality have been identified. Among these recommendations are (I) to include the interventional radiologists that will perform the collections on the clinical trial research team, (II) to establish a cross disciplinary biopsy team to communicate during clinical trial development and periodically throughout the trial to discuss success rates and research outcomes, and (III) to obtain up to five cores per biopsy when feasible to increase assay success rates. Another recommendation was to discuss each biopsy patient with the institution's interventional radiologists so the risk of the biopsy, specimen requirement and protocol specifics to ensure patient safety and biopsy success; to this end, implementation of a standard prescreening scoring system originally developed and implemented at MD Anderson Cancer Center has been recommended. Implementation of many of these recommendations within DTC has significantly improved our rate of successful biopsies (7).

The report by Parseghian and colleagues raised a critical issue of research biopsy reporting as an important element to oncology therapeutic research. Research biopsy use, or results were successfully reported only 50.8% of the time. As noted above, many components are critical to a successful research biopsy result (12-14). Successful research biopsies will lead to increased reporting of research biopsies. The authors noted that requiring a mandatory biopsy and listing a biopsy as a study objective increased the likelihood of reporting. To justify mandatory biopsies, the benefit of the results needs to balance with the risk of the biopsy. Unreported research biopsy results in clinical trials has no value and should not be performed. This reinforce the conclusion of Parseghian that results of the research biopsy, positive or negative, needs to be reported.

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