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Position Paper

Ensuring Successful Biomarker Studies in Bladder Preservation Clinical Trials for Non-muscle Invasive Bladder Cancer

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Abstract. Recent technological advances have created new opportunities for performing biomarker studies within the National Cancer Institute's (NCI's) National Clinical Trials Network (NCTN) clinical trials. These new platforms yield more robust measurements when tissue and blood handling is optimized. At the same time, there is a strong interest in banking tissue and derivatives, such as DNA and RNA, for future biomarker studies using novel platforms that may emerge during the intervening time to trial completion. The NCI recently hosted a Clinical Trials Planning Meeting focused on two trial concepts for bladder preservation in patients with high-risk non-muscle invasive bladder cancer (NMIBC) and the correlative translational research to be integrated into these trials, where experts discussed prioritization for the use of patient samples, and a framework for best practices emerged. The overall goal of this meeting report is to summarize this discussion and to provide the working group's recommendations for biospecimen handling for future bladder preservation studies.

Keywords: Tissue banking, FFPE RNA, urine tumor DNA, plasma tumor DNA

Over the past five years, there has been a change in the way biomarker studies are incorporated into NCTN clinical trials. The scientific community recognizes that tissues collected within the context of NCTN trials are a unique resource for phenotype and genotype studies and thus a public resource that should be reserved for the most robust and impactful downstream analyses. Therefore, it is now recommended that tissues and blood collected from participants in large Phase 3 and FDA registration studies be banked until the trials have achieved at least 75% accrual, and a rigorous peer review process should be in place to vet proposals for the use of these valuable patient samples [1–3]. The guiding principle is that the tissues should not generally be used for discovery science or for the validation of technological platforms and cut points that have not been robustly pre-defined; instead, discovery science should first be performed using single institution cohorts and/or archival samples contributed from multiple sites. With these priorities in mind, emphasis has shifted away from committing NCTN clinical trial specimens to experiments proposed at the time NCTN clinical trial protocols are being developed. Instead, the focus is now on using best practices for tissue storage to ensure that the maximum number of patient specimens can be analyzed using the most advanced analytic methods to test the most compelling biomarker hypotheses when sufficient outcome data is available following trial completion. Finally, adequate consent should be obtained from all participants to allow for both future biomarkers studies and deposition of raw sequencing data into public repositories for validation of results by the broader scientific community [2].

While the overall objective embodied in this approach is laudable, it presents certain challenges. First, biomolecules, particularly some proteins and RNA, have finite half-lives that can be shorter than the time required for trial accrual. Second, because the optimal tissue handling and processing best practices for future platforms cannot be predicted, there is no guarantee that banked tissues will be optimally processed and stored for use with the most innovative platforms available in the future. Finally, and fortunately for patients, the pace of drug development is

accelerating, and this is especially true in the setting of high-risk NMIBC, so post-hoc biomarker measurements can become irrelevant if the clinical regimen being studied is no longer utilized. Recent examples of biomarkers explaining negative clinical trial results (i.e. TSC1 mutations and mTOR inhibitor sensitivity, for example) underscore the importance of determining whether a drug may be highly active in a discrete, biomarker-defined subset of the patients, even if primary endpoint of the trial was negative [4, 5].

The NCI recently hosted a virtual Clinical Trials Planning Meeting to discuss two clinical trial concepts focused on bladder preservation for patients with high-risk NMIBC. A biomarkers working group was created to facilitate the design of biospecimen collection and analysis strategies. The discussion over the two-day meeting highlighted the need to establish "best practices" for these and other future NCTN clinical trials. The following is a summary of the discussion with recommendations for maximizing the impact of biomarker studies in these and other multi-site clinical trials.

We want to emphasize that this discussion focused on ensuring that adequate specimens will be available when the specific biomarker studies are planned. Those plans thus require formal statistical considerations that include timing of specimen collections, specification of clinically meaningful effect sizes or degrees of association, and the associated sample size and power calculations. These considerations are study specific; our discussions therefore focused on the acquisition and processing of specimens.

TUMOR TISSUE

There was consensus among the group members about the importance of mandating submission of formalin-fixed paraffin-embedded (FFPE) tumor tissue collected at the time of study enrollment, or, if possible, from the most recent tumor specimen available. Tumor tissue from other relevant clinical time points (such as at the time of recurrence, if applicable) should also be banked when feasible. When possible, pre-analytic variables including cold ischemic time, time in formalin and duration of storage should be recorded, as these will impact various analytes differently. Cold ischemic time (CIT) represents the period between tissue being removed from the patient and immersion in formalin, with RNA and DNA analytes remaining stable for up to 12 hours. More stringent recommendations have been issued regarding specific clinical analytes, such as breast hormone receptors, with several groups recommending CIT of less than 1 hour [6]. Time in formalin is the period of time tissue is immersed in fixative prior to processing, and ideal thresholds vary by analyte, with the minimum being 6 hours and ideal maximum of 24 hours. While not standardized across clinical labs, these ranges are usually attained based on clinical work flows for usual patient care. Generally speaking, shorter block storage time favors integrity of analytes, with RNA degrading first (recommended storage time less than or equal to one year), followed by DNA (less than or equal to 5 years) and protein remaining stable for up to 10 years [7]. Although FFPE blocks were considered ideal, the group recognized that most institutions would not release their tumor blocks and therefore that at least 15 unstained microscopic slides (5- or 10-micron thickness) should be requested to ensure sufficient tumor tissue is available for DNA and RNA extraction for downstream analyses. To reduce oxidative damage to nucleic acids, the unstained slides should be stored in vacuum sealed bags at -20° or -80° C, and a detailed description of the tissue source should be provided [8]. Optimally, informatic systems should be in place to ensure that tissue blocks maintained at enrolling institutions are preserved for future biomarker studies linked to the relevant NCTN clinical trial unless they are required for clinical diagnostic purposes.

Carcinoma in situ (CIS) is an important component of high-risk NMIBC that presents specific challenges for biomarker studies because of scant tumor tissue content. Ongoing studies are exploring the feasibility of performing bulk RNA and DNA sequencing studies on macrodissected or laser capture microdissected areas of CIS that are identified by an experienced GU pathologist. However, multiplex immunofluorescence and spatial transcriptomic approaches with single-cell resolution that are compatible with FFPE sections are new and attractive alternatives to bulk sequencing for bladder CIS, needle biopsies, and other tissue sources that contain minimal tumor content. While the broad use of these novel platforms is currently limited by their cost, plans should be made to ensure that tissues are collected on appropriate slides and processed in ways that maximize the quality of subsequent analyses using these platforms. Challenges with CIS low tumor tissue content may also be addressed through urinary analysis of cell pellets, as these tumors are known to shed whole cells (see further discussion below).

There was strong support for digitization and central pathology re-review of all H&E slides. This is particularly critical for bladder cancer studies given the frequent evidence of divergent differentiation and variant histologic subtypes, which are often not documented in clinical reports. Pathology re-review allows investigators to reach consensus on diagnosis and is also helpful when there is limited tumor content in specimens. Preferably, H&E slides would be scanned at the enrolling institution and shared with the bank electronically; alternatively, if institutions do not have the infrastructure required for high-resolution slide scanning, the slides themselves should be submitted to the bank for scanning. Recut H&E slides from all blocks associated with a given case should be provided. In addition, for the block used to prepare the unstained slides for submission to the bank, an H&E should be provided before (top) and after (bottom) sectioning the unstained slides so that the presence of the tumor on intervening slides can be confirmed. Scanned H&E images should be banked for future artificial intelligence/deep learning studies.

The group discussed concerns about biomarker stability. James Proudfoot (Veracyte) discussed his company's experience with extensive studies employing whole transcriptome RNA expression profiling using RNA isolated from old versus new formalin-fixed paraffin-embedded (FFPE) cores and unstained slides. Fresh specimens pass quality control thresholds almost 100% of the time, whereas fail rates with older samples are commonly over 30% (unpublished observations). Some proteins are also subject to rapid decay. Based on literature from the NCI's Biospecimen Research Database, the acceptable threshold for FFPE block storage is less than or equal to one year for RNA analytes. The recommendation for sectioned slides is less than 3 months when stored in ambient conditions [7]. Therefore, the group supported sample preparation for some tissue-based biomarker measurements (i.e., transcriptomics) in real-time. Some unstained slides could be used for dual RNA and DNA extraction and stored at –80°C at the bank for future bulk sequencing. Because both proposed Phase 2 trials involved immunotherapies, a robust multiplex platform designed to characterize the tumor immune landscape should be selected for real-time analyses, which could be performed at one of the lead trial sites or, if possible, by one of the NCI-supported Cancer Immune Monitoring and Analysis Centers (CIMAC) cores.

BLOOD

The group discussed collecting longitudinal plasma samples for cell-free circulating tumor DNA (ctDNA) analyses and interrogation of other potential plasma-based markers such as microRNAs and extracellular vesicles. The blood should be collected in minimum 2x 10 mL Streck Cell-Free DNA BCT tubes to maximize the likelihood that there is sufficient plasma cell-free DNA for the generation of diverse next-generation sequencing libraries. Blood should be centrifuged according to the manufacturer's instructions to obtain plasma which can be frozen in aliquots at –80°C. The associated buffy coat layer from centrifugation should be cryopreserved for white blood cell (germline) DNA isolation and/or future functional studies. Patient-matched white blood cell DNA is important for filtering somatic variants linked to clonal hematopoiesis during ctDNA analysis. Blood collected in Streck tubes is prevented from lysis for at least one week at room temperature, so blood in Streck tubes should be sent to the bank for processing [9]. One EDTA or sodium citrate tube of blood should also be collected for serum isolation (for protein analyses), and the buffy coats associated with these samples should be saved (for germline DNA analyses and studies of peripheral blood mononuclear cells). Time points should include collections before treatment, after one cycle of therapy, and at sentinel clinical milestones thereafter. Importantly, tumor derived DNA in plasma (ctDNA) is thought to reflect the presence of subclinical metastatic disease rather than bladder-localized NMIBC, which following initial resection is unlikely to have sufficient tumor mass and vascularization to produce detectable tumor molecules within typically analyzed plasma volumes. Therefore, ctDNA analyses would be performed to determine if such occult metastatic disease could be detected and is predictive of distant failure within the context of the two clinical trials discussed at the meeting.

URINE

There was strong interest in optimizing urine collection for urine tumor DNA (utDNA) analyses because recent work suggests that utDNA levels correlate closely with local disease burden. Changes in mutational patterns can be used to track clonal evolution. There was some discussion about the advantages of separating the urine supernatant from the cell pel-

let; there are some published data to suggest that measurements are more robust using the former but formal consensus was lacking at present. Trevor Levin (Convergent Genomics) discussed his company's experience optimizing urine collection for this purpose. He shared that his company's collection kits contain chelators and polymers that in their experience stabilize utDNA for at least a week at room temperature, and other commercial preservatives also appear to perform well. Longitudinal collections of urine should be performed so that the effects of each intervention can be measured. They should include a collection before transurethral resection of bladder tumor (TURBT) (if possible), a collection before and after intravesical or systemic therapy administration, and collections at sentinel clinical time points after that (for surveillance). Although consideration was given as to the optimal time of day for urine collection (e.g., first void), it was considered impractical to enforce. The group noted that experience with utDNA platforms is still relatively limited and that it would be preferable to conduct head-to-head comparisons of available and emerging platforms before committing to one for the trials discussed during the meeting. The group also recognized that urothelial field defects could make interpreting the results of these measurements challenging in the same way clonal hematopoiesis must be filtered out in plasma-based ctDNA analyses, although recent work also suggests that field cancerization of the bladder may itself be prognostic and have a role in modulating local tumor immune environments [10]. Overall, there was strong enthusiasm for integrating urine-based analyses into the design of both clinical trials given the unique opportunity in bladder cancer patients to non-invasively collect tumor-derived DNA at multiple times before and after treatment.

Urine is also currently being used for transcriptomic, proteomic and metabolomic studies. This work is mainly exploratory, so the best urine stabilization and processing practices are still being developed. The group agreed that adding divalent cation and metal chelators to the urine at the collection time and separating sediment from supernatant prior to freezing were appropriate [11]. Sediment should be resuspended in cryopreservative, and sediment and supernatant should be stored at –80°C.

Investigators are currently attempting to perform bulk and single-cell RNAseq and high-dimensional flow cytometry using urine sediment. So far, these efforts are considered exploratory, and the group expressed concern about feasibility. Investigators are also exploring whether urine extracellular vesicles (EVs, which include exosomes) contain important biomarkers. Again, these studies are considered exploratory. The investigational platforms being evaluated now should be optimized to be compatible with the cryopreserved urine sediment and urine supernatant that are currently being banked and stored at –80°C.

IMAGING

The group supported deposition of conventional CT and MRI imaging data from NCTN clinical trials into a central data repository for future radiomics studies. Imaging data should be collected and stored in accordance with the current Digital Imaging and Communications (DICOM) standard (dicomstandard.org). The group recommended that imaging data should be stored with the Imaging and Radiation Oncology Core (IROC). The group acknowledged that some site-dependent heterogeneity may be generated in these data based on the use of different hardware and institutional imaging standards. Nevertheless, it is recommended that sites be required to adhere to certain basic metrics (e.g., CT slice thickness should be ≤ 1 mm).

In addition, and specific to the proposals discussed at this meeting, there may also be an opportunity to capture images and videos during cystoscopy and TURBT for independent assessment of the quality of endoscopy and surgical resection, and for artificial intelligence and deep learning analyses. Joseph Liao (Stanford) shared his progress in performing such studies locally. A poll of the urologists attending the meeting indicated that over 75% of them would be interested in capturing cystoscopic images from patients enrolled in NCTN clinical trials. Efforts should now be launched to establish the infrastructure for multi-site cystoscopic image capture and the feasibility of aggregating these data for these purposes.

MICROBIOME

Studies across solid tumors indicate that the composition of the intestinal microbiome influences clinical responses to immune checkpoint inhibitors and probably other immune therapies. Recently published and ongoing exploratory studies have revealed microbiome heterogeneity in other sites, including the bladder and solid tumors. Therefore, comprehensive collections of samples from all potentially

relevant sources, such as stool and urine, should ideally be performed as part of NCTN clinical trials. However, optimized methods for collecting and storing these materials have not been established. The group concluded that it is probably too early to integrate microbiome sample collections and/or real-time analyses into NCTN bladder cancer clinical trials. However, if the trial leadership team is highly motivated, collecting stool samples or rectal swabs using current best practices would be reasonable.

CONCLUSIONS

The group recommended that tumor tissue submission should be mandatory for sites participating in NCTN NMIBC clinical trials, and H&E slides from all available blocks should be scanned for central pathology re-review and future AI/machine learning studies. Nucleic acids should be extracted from FFPE tumor sections and blocks. Additional FFPE tissue and blocks should be reserved for future studies and stored at –20°C or lower. Plasma should be isolated from blood collected in at least two Streck tubes, and if possible, some of this plasma should be used for immediate measurements of ctDNA, reserving at least half of the sample, when possible, for future studies. Urine collections should be integrated into all NMIBC clinical trials and other studies focused on organ preservation. If possible, the timing of urine collection should tracked, and the urine should be treated with a stabilizer at the time of collection. Some of the urine should be processed to separate urine sediment and supernatant, and some should be used for real-time measurements of utDNA. As this is emerging technology, available platforms should be rigorously evaluated over the next few years to compare their performances. Urine sediment should be resuspended in a cryopreservative that maintains cellular integrity, and urine sediment and supernatant should be stored at –80°C. Methods for collecting and storing radiographic cross-sectional and cystoscopic images should be optimized for future integration into NCTN NMIBC clinical trials. Additional research should be performed to rigorously explore the relationship between the intestinal and/or urinary microbiome and response to immunotherapy in patients with NMIBC. If current hypotheses are validated, effort should be invested in establishing best practices for collecting and storing these samples within NCTN clinical trials.

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CONFLICTS OF INTEREST

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