BIOMARKER STUDY Evaluation Guidelines

Purpose and Background

As part of its Prioritization and Scientific Quality Initiatives, the Clinical Trials Working Group (CTWG) of NCI recommended establishing a funding mechanism and prioritization process for essential correlative biomarker studies that are incorporated into the fundamental design of a clinical trial. The objective of this initiative is to ensure that the most important biomarker studies can be initiated in a timely manner in association with clinical trials.

Biological studies embedded in clinical trials often lead to scientific observations that validate targets, reduce morbidity, predict treatment effectiveness, facilitate better drug design, identify populations that may better benefit from treatment, improve accrual and retention, and ultimately lead to change in the standard of practice. Support for timely and important studies during the clinical trial concept development phase will ensure timely development of effective, informative and high impact clinical trials.

The primary purpose of this funding mechanism is to support **INTEGRAL** and/or **INTEGRATED** biomarker studies embedded in large (≥100 patients), randomized phase 2 treatment trials or in any randomized phase 3 clinical trials conducted by NCI National Clinical Trials Network (NCTN) Groups and NCI Community Oncology Research Program (NCORP).

Biomarker Studies

Two types of studies embedded in NCTN or NCORP trials are eligible for consideration – INTEGRAL and INTEGRATED.

A. **Integral Studies** - Defined as assays/tests that must be performed in order for the trial to proceed or to support the primary analysis. Integral studies are inherent to the design of the trial and must be performed on all participants, usually in real-time. The assay/test must support one of the trial's primary hypotheses. Integral studies have the highest funding priority. For example, assays/tests to establish eligibility, randomization, stratification, or treatment assignment in a treatment or QOL trial.

B. **Integrated Studies** – These are intended to validate markers for possible use as an integral marker in future trials or in clinical practice. Integrated studies should test a specific hypothesis with a preplanned statistical design and are not hypothesis-generating or exploratory. Integrated studies must be included in the protocol as a secondary objective.

   Real Time (RT) Integrated Studies -- Some integrated studies may require that assays or tests be performed during the trial, for example, biomarker assays that require a fresh tumor biopsy or real time processing of a blood or tissue sample to measure treatment response.

   Integrated RT studies should be submitted after the principal investigator (PI) receives notification by NCI's Cancer Therapy Evaluation Program (CTEP) or Division of Cancer Prevention (DCP) PIO that approved the concept, preferably within 3 months.

   Non-Real Time (NRT) Integrated Studies -- Other integrated studies do not require real time assays/tests or sample collection or processing. Examples of NRT integrated assays/tests

include gene expression studies that correlate with outcome or PD-L1 assays performed on diagnostic tumor samples where the results are not used for eligibility, treatment assignment, or treatment management.

Integrated NRT studies will be accepted only after the trial has reached at least 75-percent of the protocol-specified accrual goal and no later than six months following the date of publication of an abstract or manuscript on the primary outcome results of the trial (whichever occurs first).

An example of integrated studies are studies to establish or validate clinical utility (including cutpoints) for assays/tests that show promise for future use as integral biomarkers

Criteria for Review of Biomarker and Imaging Studies

Clinical assays/tests that are used to assign or significantly modify a patient's treatment in the proposed clinical trial must have undergone rigorous analytic validation and sufficient clinical validation to warrant inclusion in a clinical trial. Biomarker assays must be performed in CLIA-accredited laboratories (if they are reported to the patient or their physician) and may need FDA review as well. Prioritization and evaluation criteria include:

- The strength of the preliminary data for both test utility and performance characteristics including cutpoints
- Adequacy of statistical plans, including power, stringency, and subset analyses if indicated
- The potential of the test to change practice and have high impact on patient care (e.g., the impact of the test itself or the change of therapy indicated by the results of the trial)
- The ability of the test to yield well-defined and validated interpretations that will guide decision-making
- The extent of standardization of the assays/tests/tools as to be transferable to the non-research setting
- The adequacy of the process for specimen collection or image acquisition or analysis including feasibility data
- A description of cost-sharing with entities that would eventually commercialize the test

It is not intended that any priority or particular level of merit is assigned to one criterion over another but rather the proposals are evaluated based on the totality of the information and strength of the data. Based on the strength of the information presented and your scientific judgment, you will be asked to rate your level of enthusiasm for the study on a five-point scale from High to Mild.

BIQSFP submissions should include a completed Study Checklist for each assay. The completed Checklist should include a response to each element.

Please refer to the 2018 BIQSFP Guidelines *(https://www.cancer.gov/about-nci/organization/ccct/funding/biqsfp)* for additional program information.

Please complete and return the attached BIOMARKER STUDY EVALUATION TEMPLATE. Thank you.