

Administrative Supplements to Support Biomarker Studies Associated with NCI-supported Clinical Trials of Immunotherapy

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Purpose

As the NCI/DCTD-supported trials networks become increasingly involved in immunotherapy-based clinical trials, there is an urgent need to develop effective strategies and enhanced capacities for coordinated correlative studies involving immune-related biomarkers. The purpose of these supplements is to: (1) Support research teams capable of conducting biomarker studies to characterize and monitor the human immune system, tumor cells and tumor microenvironment in the context of ongoing or completed immunotherapy trials conducted by NCI trial networks (refer to: **“To qualify for this initiative, the applications should meet the following criteria”** for a listing of eligible trial networks) and (2) support both single trial and cross trial analyses to identify biomarkers that can either select patients for treatment, monitor therapeutic effects, and/or explain response or resistance.

The supplement will provide a means for laboratories to conduct biomarker studies to validate existing biomarkers as clinically useful assays and to develop novel insights into human immune system-cancer interactions. A specific focus of the supplements is to ensure that cross-trial and cross-network collaborations are established to accelerate progress, exchange tools and facilitate best practices for biomarker correlative studies in immunotherapy trials.

Eligibility Information

1. Supplemental funding will be available for active grants using the following grant mechanisms:
 - P30 Cancer Center Support Grants (CCSG)
 - P50 Specialized Program of Research Excellence (SPORE) Grants
 - U10 Cooperative Clinical Research – Cooperative Agreements for the 5 NCTN groups (both Operations and Statistical Grants)
 - U24 Resource-Related Research Projects – Cooperative Agreements for the 5 tumor banks for NCTN-supported clinical trials
 - NOTE: Because the proposed studies must be associated with immunotherapy-based clinical trials conducted by one of the following **NCI/DCTD supported clinical trials organizations**, P30 and P50 grantees are encouraged to work with investigators at your institutions who are members of these clinical trial organizations:
 - Early Therapeutics Clinical Trials Network [ETCTN],
 - National Clinical Trials Network [NCTN],
 - Cancer Immunotherapy Trials Network [CITN],
 - Pediatric Brain Tumor Consortium [PBTC],
 - Adult Brain Tumor Consortium [ABTC]
2. To be eligible for this supplement, the **parent grant** must include clinical research.

Background

For this solicitation, **immunotherapy** is defined as a treatment modality whose primary mechanism of action (MOA) is mediated through the immune system or immune effector cells. Monoclonal antibodies directed at the vasculature or tumor cell targets with MOAs through either antibody-dependent cellular

cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), or inhibition of malignant signal transduction are not considered immunotherapy for the purposes of this Supplement.

For optimal clinical development of cancer immunotherapy, there is a critical need for biomarkers that can measure the complexity of the tumor-host interface. Biomarkers have the potential to provide deeper understanding of the biology and mechanisms of drug action and to shed light on determinants of response or resistance, which may in turn provide guidance for patient selection and combination strategies. Optimal development and use of biomarkers for clinical immunotherapy trials requires the availability of fit-for-purpose assays and proper trial designs and data analysis. In view of the complexity, the value of biomarker studies for immunotherapies could be further enhanced through standardized and carefully designed databases and platforms that foster integration across clinical and biomarker datasets from individual clinical trials at multiple institutions.

This request for Administrative Supplements supports efforts to enhance the effectiveness of immunotherapy-based clinical trials through two primary aims:

Aim 1: Biomarker studies in NCI-supported immunotherapy-based clinical trials that are ready-to-proceed, ongoing or completed

Aim 2: Demonstration of the capability to integrate and analyze biomarker data and associated clinical data within and across trials using existing or adapted informatics/computational tools

Critical Requirement: For an application to be responsive to this solicitation, the application must include projects that fulfill both Aims 1 and 2.

Aim 1: Incorporation of biomarker studies in NCI-supported immunotherapy-based clinical trials that are ready-to-proceed, ongoing or completed (refer to: “To qualify for this initiative, the applications should meet the following criteria” for a listing of eligible trial networks)

This solicitation supports efforts to analytically and clinically validate potential predictive markers or to develop novel insights into human immune system-cancer interactions in the context of immunotherapeutic intervention. The scientific goals of these studies may include the validation of potential biomarkers for prediction of response, resistance, or toxicity; assessment of the pharmacodynamic impact on the tumor and the host immune system (including all components of the tumor microenvironment); assessment of pharmacogenomic effects on the host, and interrogation of the MOA/resistance of specific agents. Applicants should have assays that are fit for purpose for human samples. The technology for the assay should be currently available in clinical laboratories. If additional, limited optimization of the assay is needed, this can be included in the application but the timeline for analytic validation studies should be specific and feasible within the supplement period.

The types of projects may include but are not limited to the following:

- Projects that involve **clinical validation of biomarkers to predict** therapeutic outcomes are of the highest priority. Proposed projects must utilize specimens from NCI-supported clinical trials networks (refer to: “**To qualify for this initiative, the applications should meet the following criteria**” for a listing of eligible networks). An expected outcome of the project should be all of the following: i) adequate demonstration of the association of the result of the assay with a clinical endpoint (e.g., survival, response, toxicity, disease presence or absence) utilizing samples from patients who have been treated or exposed to a uniform therapeutic intervention. Validation should include i) clinical sensitivity and specificity or association of the assay result with the defined clinical endpoint, ii) estimation of the prevalence or distribution of the

biomarker within subjects or patients for the intended clinical context, and iii) establishment of an appropriate cut-off or threshold (if applicable) for the assay using appropriate statistical analyses.

As a prerequisite to clinical validation, assays should be analytically validated to establish the following (as applicable): (i) accuracy, (ii) precision, (iii) analytical sensitivity, (iv) analytical specificity including robustness to interfering substances, (v) reportable range of test results for the test system, (vi) reference intervals (normal values) with controls and calibrators, (vii) harmonization to achieve reproducibility if the assay is to be performed in multiple laboratories, (viii) standard operating procedures (SOPs) for appropriate quality control measures. Assays that support medical-decisions such as treatment decisions (**integral biomarkers**) will need to be optimized to perform according to the highest clinical standards with rigorous quality monitoring in CLIA-certified laboratories.

- Biomarker studies in early to late clinical trials for **assessment of treatment effects on tumor-host interactions or exploration of mechanisms of action/resistance** that inform future biomarker studies are also encouraged. The proposed biomarkers may be derived from biomarker discovery research or can arise from evaluations of pre-clinical hypotheses. The stated goal of the study should include how the proposed biomarker study might enhance the understanding of immunobiology in a clinical context and/or facilitate further development of a particular immunotherapy or class of immunotherapies.

Even when the biomarkers are considered exploratory for purposes of generating new hypotheses, the assays used should have performance sufficient to meet the analytical standards necessary to ensure confidence for addressing the research question and be fit for the intended use.

- Studies using **imaging as biomarkers** (e.g. mapping of specific immune cells in tumors) as a means to monitor response to immunotherapies in clinical trials will also be considered. Strong preclinical data should be presented to support the potential for correlation between the imaging signal and immune features of the tumor microenvironment. Applicants can propose imaging biomarkers in their applications but they are not required to do so.

*While not required, proposals for immunotherapy biomarker interrogations in those tumors considered “recalcitrant” such as pancreatic cancer and small cell lung cancer are encouraged in this initiative.

Examples of potential proposals from eligible trials could include, but are not limited to:

- *Analyses of subsets of immune cell subpopulations in tumor and blood: frequency, phenotype, expression of key molecules*
- *Measurement of the magnitude of Type I immune response: function, activation, suppression*
- *Genomic analyses of tumor and microenvironment: mutational load, relevance of neoantigens, T cell diversity*

Aim 2: Demonstration of the capability to integrate and analyze biomarker data and associated clinical data within and across trials using existing or adapted informatics/computational tools

As large and complex data sets become available to the immune-oncology research community, new opportunities to interrogate these data for biomarker discovery have become a reality. However, these data sets have not yet reached their full potential for identification of biomarkers and their translation to assays for clinically meaningful immunotherapy biomarkers. There is a need for facile informatics approaches for data collection, access, and cross-trial integration of complex, multi-component

biomarker information. There is also a need for computational methodologies to facilitate interpretation of these complex data sets to gain important biological and clinical insights. Algorithms to derive multimodal signatures integrating various types of molecular tumor data (i.e., high throughput mutational data, immunohistochemical analyses and functional data) with tumor microenvironment factors also need to be developed and implemented in clinical trials. Proposals in this area may include:

- Novel analyses and/or data integration efforts may be conducted to interrogate existing databases for biological and correlative questions. The data types may include phenotypic, genomic or other 'omic, and functional imaging measurements as well as clinical outcomes, and should be derived primarily from immunotherapy clinical trials from DCTD/CTEP treatment trials networks. Data obtained from ongoing or completed studies is permitted. Use of preliminary data from non-NCI-supported trials to support the planned analysis on NCI-supported trials is also permitted. The objectives of the analysis may include evaluation of immune and tumor interactions, readout of drug mechanism or toxicity, or identification or cross-validation of predictors of clinical outcomes.
- A critical component of Aim 2 proposals is the demonstration that awardees conducting biomarker research on the same or separate trials can work together cooperatively to harmonize their efforts with other selected centers to perform cross-site and cross-trial analyses. If selected, the awardee will be required to team with other awardees to develop joint projects and analysis plans, and must also agree to participate in the development of standard operating procedures for key assay platforms, data management and other methodologies as appropriate.
- The integration efforts should include use and/or adaptation of existing informatics or computational tools to accomplish the objectives of the proposed analyses. The applicants should address how the data could be made broadly available to outside researchers, based upon NIH Data Sharing guidelines (http://grants.nih.gov/grants/policy/data_sharing/place). However, tool development *per se* for Big Data Science and systems biology for nonspecific use in future studies are outside the scope of this supplement and should not be proposed.

Examples of project types that could be considered include, but are not limited to:

- *Building database platforms and entry standards for selected platforms that can be used for data submission across DCTD/CTEP-supported trials*
- *Proposals to enable more efficient and effective methods for data integration:*
 - *Approaches to create connections across data types, e.g. Omics data (e.g., genomics, proteomics, immune phenotype, etc.)*
 - *Integration of predictive biomarkers for immunoresponse or toxicity with clinical data*
 - *Imaging and physiological data (e.g., CT, PET, cellular imaging etc.)*
- *Development of approaches for modeling, simulation, or analysis to produce more useful biomedical information:*
 - *Multidimensional statistical and computational methods for analyzing high-dimensional data*
 - *Algorithm development for clinical decision making: personalized immunotherapy*

To qualify for this initiative, the applications should meet the following criteria:

- The objectives of the proposed study should be achieved within a period of 1 year. However, NCI will consider a request for additional time, if needed, at the end of the year.
- The proposed projects must fit within the scope of the parent award

- The proposed studies must be associated with immunotherapy-based treatment trials within DCTD/CTEP-supported clinical trial networks. The clinical trials that qualify MUST be conducted by one of the following organizations:
 - Early Therapeutics Clinical Trials Network [ETCTN]
 - National Clinical Trials Network [NCTN]
 - Cancer Immunotherapy Trials Network [CITN]
 - Pediatric Brain Tumor Consortium [PBTC]
 - Adult Brain Tumor Consortium [ABTC]
- * Note: Contact information for the leadership of the clinical trials groups that qualify can be found at: <http://ctep.cancer.gov>.
- *NOTE: The clinical trials on which biomarker proposals are based should be completed/closed-to-accrual, ongoing, or ready-to-proceed (“ready to proceed” is defined as: FULL IRB approval should be in place for the clinical trial by the time of the Award. Funds will not be released until full IRB approval for the clinical trial is obtained.)
- Principal Investigators of the parent award are encouraged to work with laboratories at their site that have experience in immunologic biomarker studies.
 - Applicants must demonstrate by a letter of support from one or more the authorized trial organizations that they have access to the clinical samples and/or data necessary to propose studies under Aims 1 and 2 above.
 - Biomarker efforts associated with this solicitation should be applicable for use on **human specimens** or directly in humans.
 - Proposals should not be duplicative with ongoing or previous studies.

Investigators’ Team

The projects proposed for this supplement require multi-disciplinary interaction to accomplish the design, execution and analysis of the biomarker studies. Therefore, in addition to the PD/PI, the Investigators’ Team may include the following participants:

- *Clinical Investigator*: Investigator(s) who define the intended clinical context of use for the marker and its assay and will oversee their incorporation into a potential trial – likely to be oncologist(s) who treat patients, but may also be a translational scientist.
- *Clinical Laboratorians*: Investigators are required to demonstrate expertise in development of biomarker assays (e.g. molecular or clinical pathologist, molecular laboratory scientist)

If the biomarker assays are intended for medical decision-making, they should be prepared for use in a CLIA-certified clinical laboratory. Alternatively, if an assay is to be used for evaluation of biological hypotheses or putative mechanism of action (not for medical decision making in the current study) research laboratory standards of quality are acceptable.
- *Statistician/informatician/computational scientists*: Team members should be familiar with the methodology of marker studies. They should be capable of providing support for statistically valid design of studies and for selection and application of appropriate statistical analysis methods and computational and bioinformatics algorithms for assessment of the performance of the biomarker within the intended clinical context.

- *Commercial Developer* (optional): While not necessary, collaboration with a commercial partner who will support the clinical development and commercialization of the assay is encouraged.

Terms and Conditions of Funding and Allowable Costs: The budget should justify all the direct and indirect costs. Up to **\$750,000** in total costs will be available for each supplement. The award period will be for 1 year; however, NCI will consider a request for an unfunded extension of the project if needed.

(Note: NCI expects to award up to 10 supplements).

Supplement Award Application Procedures

1. **Cover letter:** Prospective applicants are asked to submit a letter of intent that includes the following information:
 - i. Title and grant number of the parent grant
 - i. Names of other key personnel
 - ii. Name of the contact person of this project
 - iii. Participating institution(s)
 - iv. Number and title of this funding opportunity

2. Application

- a. Standard PHS 398 (pgs 1-6)
 - i. Item 2: check yes and provide the title indicated in the cover letter, 1.b.
 - ii. Item 7A-8B, denote the direct and total costs for the project. Total costs may not exceed \$750,000.
 - iii. The authorized organization representative must sign the face page.
 - iv. Include a detailed budget description.
 - v. Provide NIH biographical sketches for key members of the team not already provided in the parent grant.

- b. **Summary of the Project.** On 8 pages or less describe:

Specific Aims: Describe the specific aims of the research project. Please indicate how the aims of the project fulfill Aims 1 and 2 of this Supplement.

- i) Background and Significance
 - Define the cancer problem to be addressed, including the marker(s) and methods for detection and how they fit the intended clinical context in which they may be used.
 - Provide the biologic and immunologic rationale for the marker(s) and its potential implications to scientific understanding and/or development of immunotherapy.
- ii) Preliminary Data
 - Describe the current state of analytical validation of the assay or method of detection in human specimens within the intended clinical context, including the current reagents and technologies and types of specimens that the assay will use (e.g., fresh frozen or formalin-fixed tissue, serum or plasma)
- iii) Approach (describe applicable elements)
 - Plan for clinical use of the biomarker within one or more immunotherapy clinical trials.
 - Provision of a statistical justification (e.g., power analysis) for the number of specimens needed

- Plans for additional optimization of analytical performance to establish that the assay is fit-for-purpose. Some validation should have already been accomplished so that remaining optimization requirements are limited to more minor adjustments such as establishing or refining cutpoints for the assay.
 - Plans to accrue specimens to perform the biomarker studies including identification of the clinical resource or trial that will provide specimens, documentation of appropriate availability and pre-approvals to obtain specimens (i.e., indication that the repository holder identifies availability of specimens and that there is an appropriate process to obtain the specimens with reasonable certainty)
 - Identification of Potential Pitfalls and Alternative Approaches to overcome obstacles
 - Describe how the institution and principal investigator will function in the context of a clinical laboratory consortium where methodologies could be jointly developed and analyzed among the applicants selected for these supplements
 - When used for clinical (or investigational) decision making within clinical trials, describe plans to address the regulatory requirements (e.g. Investigational Device Exemption) regarding use of the biomarker assay in clinical trials, including evaluation of significant risks associated with use of the assay and biomarker within the context of a clinical trial.
 - Discuss legal issues relating to the possibility of controlling intellectual property and plans for collaboration with commercial entities to support the assay.
 - Demonstrate how the data will be analyzed, shared with other awardees (to be named by NCI) and eventually made more broadly available to the research community using existing clinical and biomarker data from the treatment trial(s) described above or using other existing clinical and biomarker data from DCTD/CTEP-supported network trials. Also, describe how the data could be used to perform cross-trial and cross-site analyses.
- iv) Milestones and Timeline
- A timeline including milestones is required.

Review Criteria

Applications will be administratively reviewed internally by NCI. Review of the applications will be based on: Responsiveness of the application to both aims 1 and 2; Team and site organization; Scientific rationale, as well as feasibility and appropriateness of the research plan in the given clinical trial context; Availability of fit for purpose assays; Potential implications for scientific understanding or drug development; and Supportive letters of collaboration with one or more of the eligible DCTD/CTEP supported trial networks. The applicant needs to demonstrate the ability to perform biomarker analyses in one or more treatment trials and also demonstrate the ability to manage and analyze the data collected, share it with other collaborators (to be named by NCI based on the selected projects and awardees) and commit in the application to participate in cross-study analyses with other supplement awardees.

Review Process:

Biomarker studies that are approved via this supplement award will be **“exempted”** from the required DCTD/CTEP review process for network-funded trials. For example, ETCTN trials will not have to undergo review by the NCI Biomarker Review Committee (BRC) and NCTN trials will not have to be reviewed by the NCTN Correlative Science Committee or the Protocol Review Committee. However, all biomarker study plans still need to undergo review and approval by the DCTD/CTEP Protocol Review

Committee before the supplement funds can be utilized, and interaction between the awardees and NCI staff is expected.

Budget

NCI will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research. If the network trials permit specimen collection, shipping and/or biopsy costs in the parent grant for the trial, then funding should not be requested in this supplement for these procedures. Only when funds are not available from the parent grant for the required specimen collection is the applicant permitted to include these costs in the supplement request.

Awards

Awards will be based on responsiveness to Aims 1 and 2 of this announcement and the availability of funds.

Reporting Requirements

Information on what has been accomplished via the administrative supplement during the funding period should be included in the progress report for the parent grant. Terms of award may also include milestones that will periodically be reviewed with the grantee by the NCI staff to provide assistance to the grantee, and to ensure progress toward achieving Aims 1 and 2.

Contacts for Scientific Questions:

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Submission Directions:

The grantee institution, on behalf of the PD/PI of the parent award, must submit the request for supplemental funds directly to NCI. Submit a signed, typewritten original of the application, preferably via e-mail in an attached pdf, or via regular mail to:

Crystal Wolfrey
Office of Grants Administration
National Cancer Institute
9609 Medical Center Drive, Rm 2W472
Bethesda, MD 20892 (regular mail)
Rockville, MD 20850 (hand delivered mail)
Crystal.wolfrey@nih.gov