Letter of Intent (LOI) Basics

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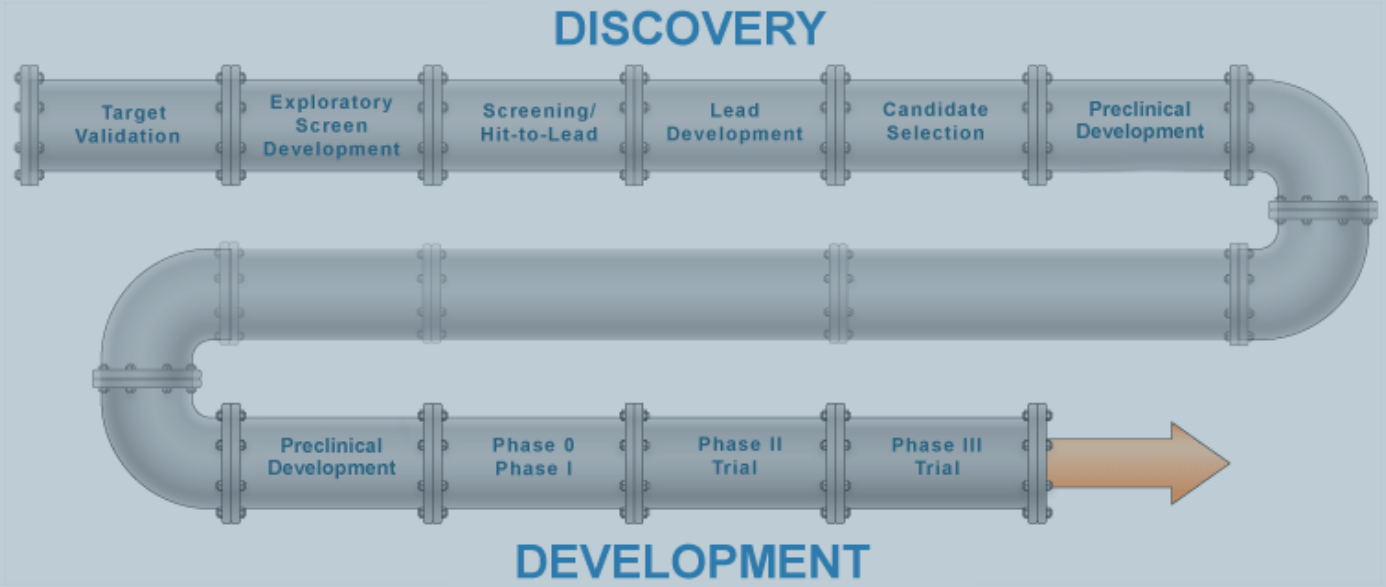
Letter of Intent (LOI) as Team Science

Cancer Therapy Evaluation Program (CTEP)

NCI: Partnerships with Industry and Academia for Cancer Drug Development

- **For over seven decades,** NCI has done drug development and discovery in the public interest.
- **For over five decades**, NCI has coordinated relationships between Industry and Academia to help develop new cancer drugs.

- In the current iteration of this effort, two programs run in sequence to manage a portfolio of partnerships between NCI and Industry or Academia.
- **NCI Experimental Therapeutics (NExT) Program** is the program that selects agents for NCI-sponsored pre-clinical and clinical development.



- The **Experimental Therapeutics Clinical Trials Network (ETCTN)** is the clinical trials network that performs clinical studies of agents that are approved through NExT.
- In these partnerships, NCI
  - Assumes the regulatory responsibility for the trials (IND holder);
  - Pays for the clinical trials through cooperative grants (UM1) to ETCTN clinical trial sites;
  - Works with ETCTN investigators and industry/academia partners to formulate the clinical development plan for the agent.

NCI: Advantages for Industry to Co-Develop Agents with CTEP through the NCI Experimental Therapeutics Program (NExT)

- CTEP has **access** to novel agents from industry competitors, and therefore, can act as an honest broker for novel drug combination studies
- Industry realizes that there are potential therapeutic indications that **do not have high enough priority** to compete for limited corporate resources
- CTEP can **expend** public funds for clinical trials and regulatory support to advance the development of agents owned by industry
- CTEP has a **network** of experienced early-phase clinical trial investigators engaging its centralized clinical trial support systems
- CTEP **invests** in correlative science studies to explore the pharmacodynamics of agents in clinical studies

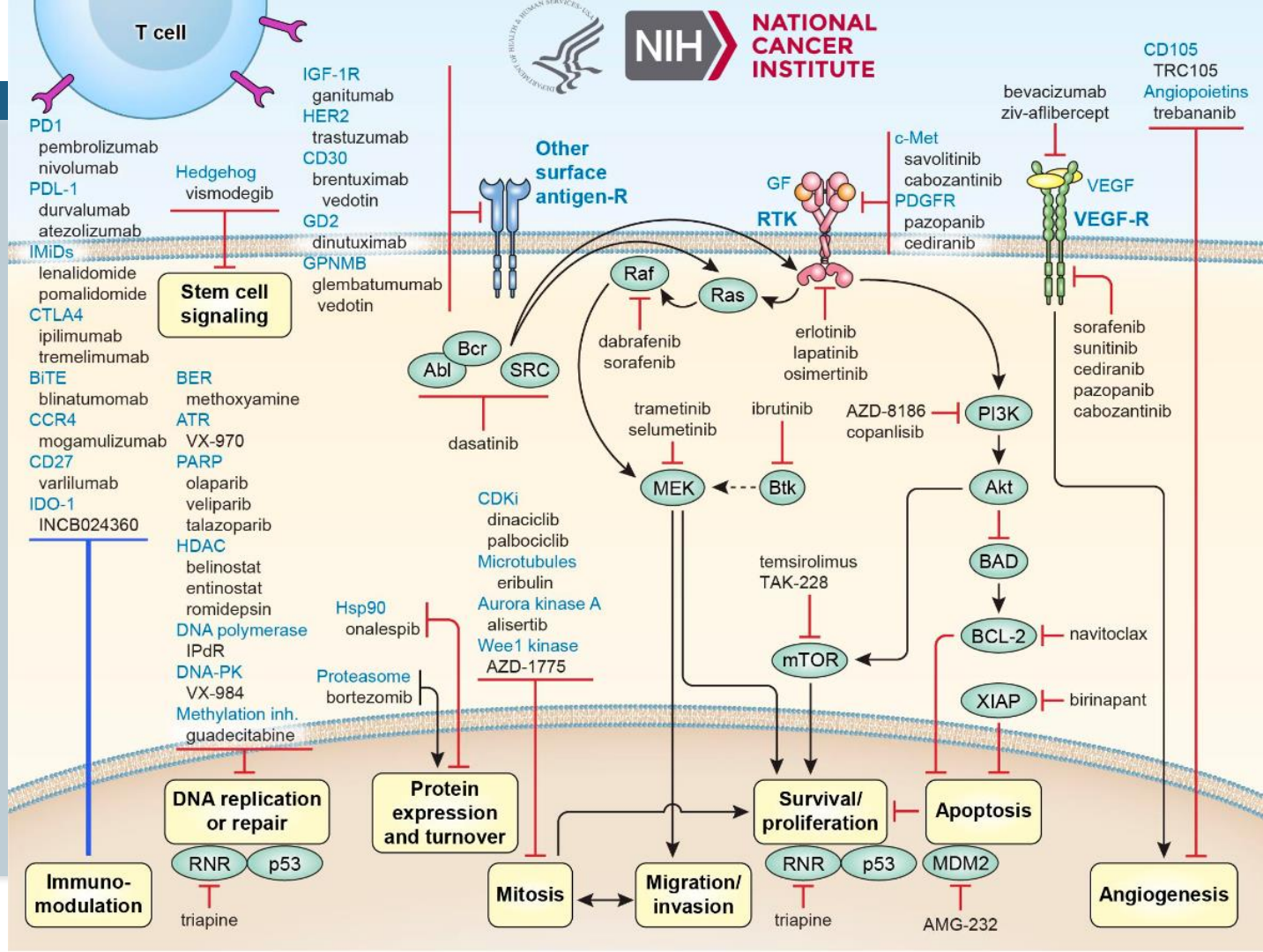
NCI: Why Extend Effort to Assist Industry Develop Its Agents

- NCI recognizes that there is a **significant public interest** in finding indications for new oncology drugs beyond those that may be the most profitable

- NCI can **advance the understanding of cancer biology and treatment** through carefully designed clinical trials and through the correlative studies that are frequently and extensively incorporated into CTEP-sponsored ETCTN trials

CTEP: Current Portfolio

- 72 active agents under cooperative research and development agreement (CRADA)
- https://ctep.cancer.gov/industryCollaborations2/agreements_agents.htm



CTEP: Letters of Intent (LOIs) as tools for TEAM SCIENCE

- Allows for collaborative, cross-cutting oncology field approach to clinical trial research
- Brings together multi-disciplinary expertise for preclinical and clinical research
- Enhances the potential for high impact oncology research by driving innovative treatments to patients in a timely manner
- Enhances the probability of accurate interpretation of clinical data
- Promotes team building now and in the future
- Overcomes obstacles often related to scientific sophistication and disease field specialization
- Changes the way investigators collaborate

Team Science

44% CTEP LOI approval rate

CTEP: Centralized Letter of Intent (LOI) Pathway Submission

- There are two paths for CTEP support of clinical development ideas—Project Team LOIs or Unsolicited Trial LOIs.

PHASE 1, 2, or 1/2
LETTER OF INTENT
Submission Form v8.1

National Cancer Institute
Division of Cancer Treatment and Diagnosis
Cancer Therapy Evaluation Program

To complete the form electronically, use the mouse pointer or the Tab key to navigate. Select and enter text for each text field.

Lead LAO/Group/Institution[1]:	[Click and enter Lead LAO/Group; use Institution for non-ETCTN/non-Group trials]
Lead LAO/Group/Institution Code[1,2]:	[Click and enter Lead LAO/Group Code; use Institution Code for non-ETCTN/non-Group trials ONLY]
Other LAOs or Trial Team Sites[1,2]:	[Click and enter other LAOs, other Groups, and any non-LAO/non-Group Clinical Site/Institution Codes; list sites outside USA separately by country. If trial will involve all ETCTN LAOs, write "All ETCTN LAOs" (no codes needed)]
Title of LOI :	[Click here to enter Title]
LOI Version Submission Date:	[Click here to enter Date of submission to PIO]

Agent Information[2] *(duplicate rows as needed)*:	Name	NSC #	Source	Investigational?
Agent #1:	[Click and enter Agent Name]	[Click and enter NSC]	[CTEP IND, Commercial, or Other]	[Y or N]
Agent #2:	[Click and enter Agent Name]	[Click and enter NSC]	[CTEP IND, Commercial, or Other]	[Y or N]
Agent #3:	[Click and enter Agent Name]	[Click and enter NSC]	[CTEP IND, Commercial, or Other]	[Y or N]
Agent #4:	[Click and enter Agent Name]	[Click and enter NSC]	[CTEP IND, Commercial, or Other]	[Y or N]

Tumor Type: *(Click within the [[ ]] and type 'x' to indicate the tumor type)*	[[ ]] Solid Tumor [[ ]] Hematologic Malignancy (NOS) [[ ]] Disease-Specific
Disease-Specific[2]: *(Specify the Name and Code of the Study Disease)*	1. [Click and enter Disease Name] [Click and enter Disease Code] 2. [Click and enter Disease Name] [Click and enter Disease Code] 3. [Click and enter Disease Name] [Click and enter Disease Code]
Phase of Study:	[Click and enter Study Phase]
Estimated Monthly Accrual: *(Note: Projected accrual rates should be realistic. Actual accrual will be monitored and measured against this accrual estimate, and failure to meet accrual goals may result in study closure.)*	[Click and enter Accrual]
Proposed Sample Size:	Minimum: [Click and enter Size] Maximum: [Click and enter Size]
Earliest date the study can begin:	[Click and enter Date]
Projected Accrual Dates:	[Click and enter Date] to [Click and enter Date]

- The better composed an LOI, the easier it is on the ETCTN centralized protocol writing service (CPWS) to write your initial protocol and the easier it is on you to supply requested content.
- Competitive LOIs contain:

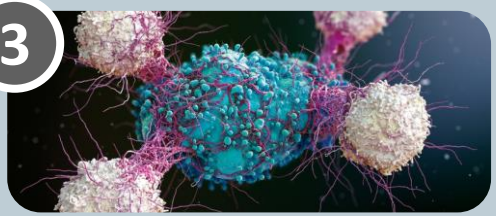
1

Test combinations in two disease-relevant cell lines

2

Test combinations in two disease-relevant xenograft models

3



Concise biomarker plans for integral, integrated, or exploratory assays inclusive of tissue, timing, funding

4

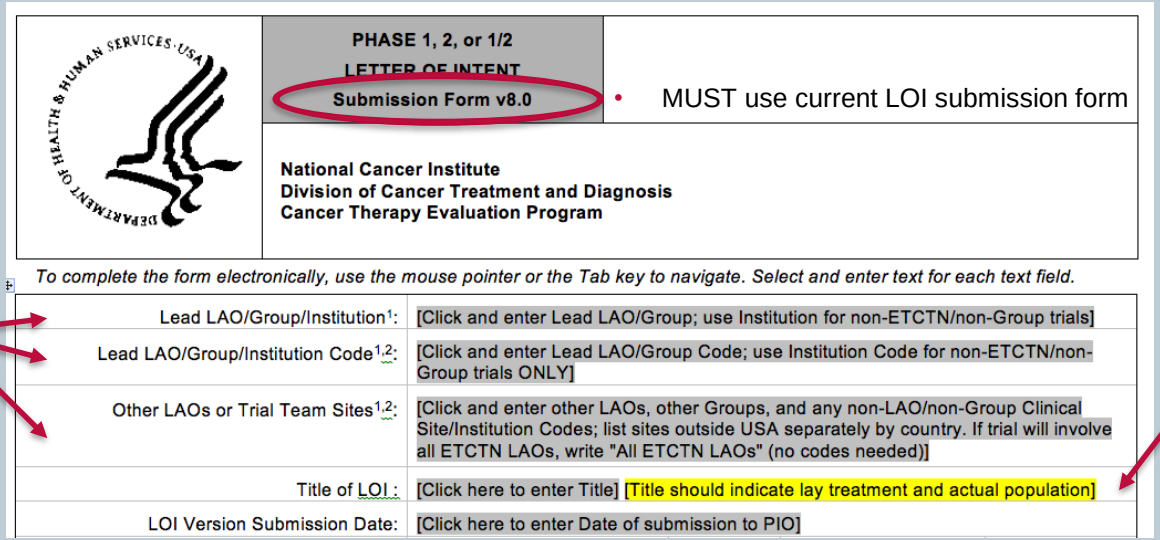
Supported experimental agent rationale in study disease cohort, with reasoned agent dose & schedule & duration

Recognized Letter of Intent (LOI) Pitfalls

Cancer Therapy Evaluation Program (CTEP)

CTEP: Recognized Letters of Intent Pitfalls

- Letters of Intent (LOIs) must be written on the current LOI Submission Form
  - Found here: https://ctep.cancer.gov/protocolDevelopment/lois_concepts.htm
- For the remainder of the slides in this deck, the following conventions will be used:



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LETTER OF INTENT
Submission Form v8.0

National Cancer Institute
Division of Cancer Treatment and Diagnosis
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To complete the form electronically, use the mouse pointer or the Tab key to navigate. Select and enter text for each text field.

Lead LAO/Group/Institution[1]:	[Click and enter Lead LAO/Group; use Institution for non-ETCTN/non-Group trials]
Lead LAO/Group/Institution Code[1,2]:	[Click and enter Lead LAO/Group Code; use Institution Code for non-ETCTN/non-Group trials ONLY]
Other LAOs or Trial Team Sites[1,2]:	[Click and enter other LAOs, other Groups, and any non-LAO/non-Group Clinical Site/Institution Codes; list sites outside USA separately by country. If trial will involve all ETCTN LAOs, write "All ETCTN LAOs" (no codes needed)]
Title of LOI :	[Click here to enter Title] [Title should indicate lay treatment and actual population]
LOI Version Submission Date:	[Click here to enter Date of submission to PIO]

- MUST use current LOI submission form
- Yellow highlighted text indicates suggested clue for competitive CTEP LOI
- Indicated CTEP LOI content domain

CTEP: Duplication

- CTEP reviews about 175 new Letters of Intent (LOIs) each year
  - As a steward of American public funds, CTEP must avoid duplicative clinical trial investigator effort
  - CTEP suggests discussing ideas with medical officers and searching https://clinicaltrials.gov as a check for duplicative effort

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Title of LOI :	[Click here to enter Title] [Title should indicate lay treatment and actual population]
LOI Version Submission Date:	[Click here to enter Date of submission to PIO]

- CTEP checks whether proposed trial is duplicative.

- An average of 2.5% of eligible cancer patient participate in clinical trials each year
  - CTEP monitors accrual pace to its active clinical trials

- CTEP checks whether proposed trial hits an indicated estimated monthly accrual.

Phase of Study:	[Click and enter Study Phase]
Estimated Monthly Accrual: (***Note**: Projected accrual rates should be realistic. Actual accrual will be monitored and measured against this accrual estimate, and failure to meet accrual goals may result in study closure.)*	[Click and enter Accrual] [Accrual should be single integer and realistic based on prior history of accrual pace]
Proposed Sample Size:	Minimum: [Click and enter Size] Maximum: [Click and enter Size]
Earliest date the study can begin:	[Click and enter Date]
Projected Accrual Dates:	[Click and enter Date] to [Click and enter Date] [Calculated: true accrual pace]

- Forecast a 'true' accrual pace for your trial and then bracket the accrual dates appropriately.

- Letters of Intent (LOIs) submitted by early career investigators (< 7 years from oncology training) and their mentors have a competitive advantage in the CTEP decision-making process
  - A preliminary teleconference between the study team and CTEP medical officer is a MUST

- LOIs designated as a career development LOI have advantage.

Is this a Career Development LOI (CrDL)?	[Click and enter Y or N] [CrDL projects fit mission of training next generation of clinical-translational science investigators] Further information and instructions regarding the submission of a Career Development LOI (CrDL) may be found at http://ctep.cancer.gov/protocolDevelopment/letter_of_intent.htm#instructions *Note: If "Y," provide the mentor's name below. The CrDL PI and mentor must schedule a call with the IDB agent monitor(s) prior to LOI submission.*
If yes, please attach and check off the following:	PI curriculum vitae [[ ]] Institutional letter of commitment [[ ]] Mentor letter of commitment [[ ]]

CTEP: Avoid Rationale Pitfalls

- Elaborate on therapeutic need in Americans

- Detail human experience with proposed agent

Rationale and Background: *(This section should provide the study rationale and supporting preclinical and/or clinical data and also address the following: what is the unmet need, why the patient population was chosen, why the drug or drug combination was chosen and any potential safety concerns with the drugs or drug combination, and how the study results might impact future trials/practice. Preclinical data supporting the proposed study should be presented, and not merely referenced. The background information should be limited to what is relevant to the proposed study and should be presented succinctly but with sufficient detail to enable evaluation by the reviewers. Avoid indiscriminate cutting-and-pasting from investigator brochures, trial solicitations, or other CTEP communications.)*

[Paragraph #1: what is the unmet need for world population and specifically for Americans] [end paragraph on targeted patient population need]

[Paragraph #2: why is the drug or drug combination chosen?] [include mechanism of action, achievable human drug concentration range, achievable T½ and estimated duration of desired drug effect, what is desired sequence of agent + agent {drug or radiation} combination study, what aspect of targeted population is anticipated to be favorably manipulated by this study]

[provide Table or Figure describing two (2) or more cell lines of disease interest showing desired drug alone or agent + agent {drug or radiation} effect]

[provide Figure describing vehicle, agent alone, agent + agent {drug or radiation} growth inhibition over time in a disease of interest xenograft (preferably two (2) or more patient-derived mouse model {but other models acceptable}]

[Paragraph #3: has the drug or drug combination been given to humans before?] [describe prior trial experience (especially cooperative group studies) by stating dose-schedule of drug or drug combination, safety concerns, any efficacy] [how does this relate to targeted patient population need] [how would results impact future clinical practice]

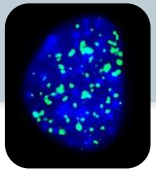
[Paragraph #4: provide background data on biomarker for the planned study, preferably an assay where you already have experience and intra- & inter-assay reproducibility]

[Paragraph #5: provide a sentence indicating the very next desired step in clinical development, especially if a cooperative group is to be involved]

- Explain how your promising new cancer treatment is to be rigorously compared to best available treatments in a hypothesis-driven clinical trial

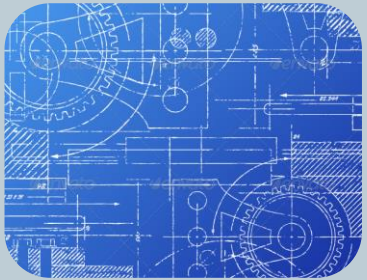
- What biomarker is planned, if any?

- What is a considered next step?



CTEP: Design

- **A well-stated rationale and hypothesis:**
  - Cancer X is known to over express the Q receptor in 75% of specimens sampled from patients who have a recurrence after definitive regional therapy.
  - Drug A binds to and inactivates the growth stimulating effects of receptor Q, and in multiple animal tumor models of cancer X, drug A has been shown to have twice the tumor shrinkage rate as commercially available drugs, and cures 30% of all mice treated.
  - ***Therefore,*** we hypothesize that drug A will demonstrate an overall response rate of at least 30% by RECIST when administered to chemotherapy naïve patients with cancer X, whose cancers have recurred following regional therapy, compared to Y% who historically respond when treated with commercially available drugs.



Abbreviated Eligibility Criteria: *(Provide key inclusion criteria. These should include patient age, performance status, whether abnormal organ function is permitted [if Yes, list only abnormal organ function parameters], permissible and required prior therapy, tumor type, and integral markers, if applicable.)*

[Click and enter Eligibility Criteria] [Enter as Table and minimize eligibility criteria to broaden studied patient population]

Study Design: *(Succinctly describe the general study design. If applicable, describe randomization and/or stratification. A schema or flow diagram may be used, if appropriate. If the trial involves biomarker studies, the Biomarkers Table below **must** be filled out according to the instructions. Appendices detailing the biomarker assays may be required as well. Please read the instructions carefully.)*

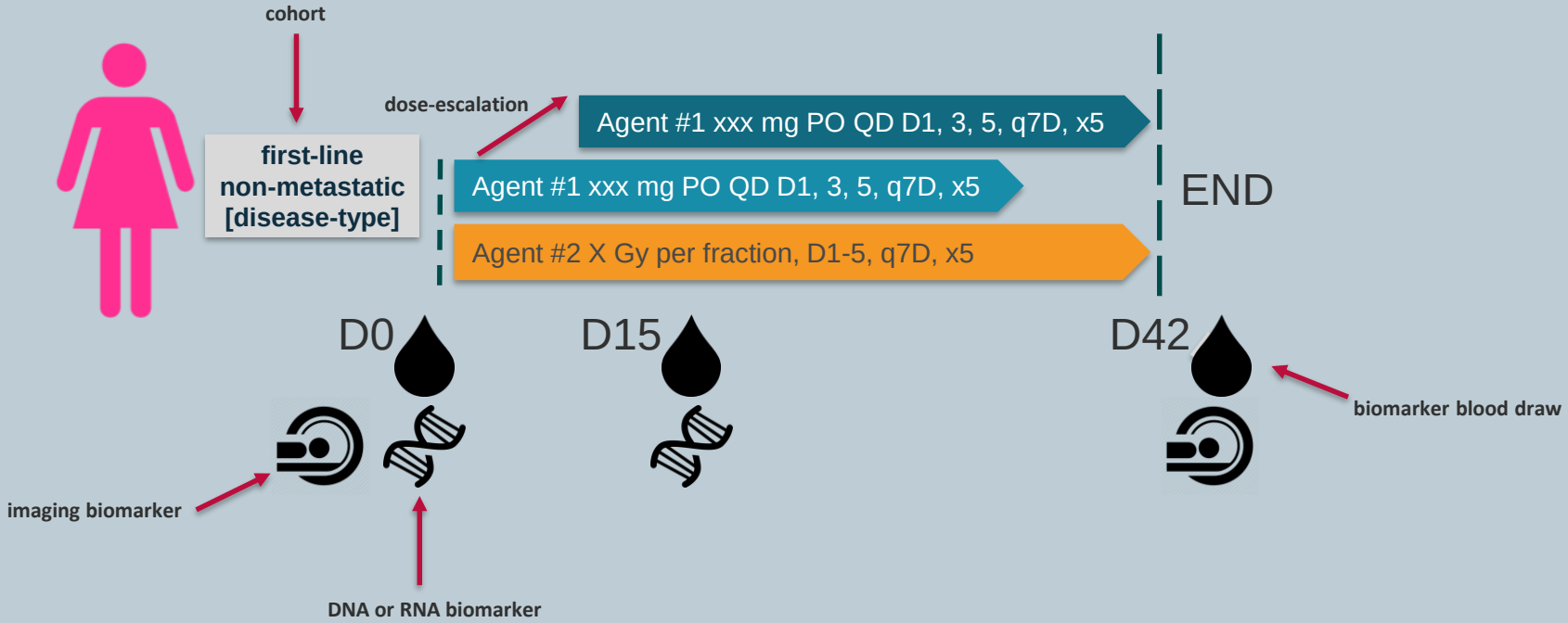
[Click and enter Study Design] [Provide picture of overall schema or flow diagram and any time tissue/blood acquired]

Treatment Plan: *(State the dose, method of administration, and schedule of each drug, and, if phase 1, provide the dose escalation scheme, and definitions of DLTs. State the duration of treatment, the duration of the study, and the duration of follow-up.)*

[Click and enter Plan]

CTEP: Pictograph for Design

- **CTEP recommends including one (1) pictograph describing patient workflow through an early phase clinical trial.**
  - **For example:**



- **A well-positioned biomarker table:**
  - Prioritizes biomarkers of interest relative to tissue or blood needed
    - Clearly indicates Use and Purpose and status of mandatory [M] or optional [O] tissue or fluid acquisition
    - Indicates Funding

Biomarkers Table*

Biomarker Name[a] AND Lead PI and Site	Assay (CLIA: Y/N)	Use (Integral, Integrated, or Exploratory)AND Purpose [b]	Tissue/Body Fluid Tested and Timing of Assay	M/O	Funding Source(s) [c]
[Click and enter Biomarker(s)] [Click and enter Lead PI/Site] [Click and enter e-mail address]	[Click and enter Assay] CLIA:	Integral: is either an endpoint of trial or triage selection biomarker [Click and enter Purpose]	[Click and enter Tissue/Fluid] [Click and enter Timing]	[M]	[Click and enter Funding Source] BRC review a must
[Click and enter Biomarker(s)] [Click and enter Lead PI/Site] [Click and enter e-mail address]	[Click and enter Assay] CLIA:	Integrated: test hypothesis that is critical to the analysis of drug or drug combination effect [Click and enter Purpose]	[Click and enter Tissue/Fluid] [Click and enter Timing]	[M/O]	[Click and enter Funding Source] BRC review eligible
[Click and enter Biomarker(s)] [Click and enter Lead PI/Site] [Click and enter e-mail address]	[Click and enter Assay] CLIA:	Exploratory: desired biologic endpoint [Click and enter Purpose]	[Click and enter Tissue/Fluid] [Click and enter Timing]	[M/O]	[Click and enter Funding Source]

** Insert additional rows as needed.*

Discussing planned biomarkers with Cancer Diagnosis Program (CDP) scientists helps ensure accuracy of this table and the rigor of intended assays

complex symptoms make cancer molecular diagnoses challenging

50% of cancer patients do not benefit from prescribed therapy

identification of novel biomarkers differentiate disease responses

CTEP: Statistical Endpoint

Endpoints/Statistical Considerations: *(State explicitly the null and alternative hypothesis(es) for the primary objective(s). Also state the sample size and associated type I and type II errors. Provide an analysis plan for both primary and secondary objectives, including correlatives. Include information about which statistical tests will be applied. State the projected accrual rate and ensure that the accrual goals are realistic and achievable with current resources. If the trial will be an ETCTN trial involving 3 or fewer LAOs, then this proposal's accrual goals must be supported by letters of commitment from each participating institution [see **Appendix A**].)*

[Click and enter Endpoints]

- Commonly used endpoints in CTEP trials

phase 1 trials: safety & phase 2 dose

phase 2 single-arm: response rate

phase 2 randomized: progression-free survival

Discussing planned biomarkers with Biometric Research Program (BRP) statisticians helps ensure accuracy of your endpoint considerations and the rigor of intended statistics

CTEP: Letter of Intent (LOI) Basics Conclusion

- LOI writing helps **formulate ideas and thoughts** about innovative clinical research
- LOI writing aids in developing **expertise** in a disease-specific area
  - Aids discussions regarding proposed concepts with peers and industry representatives
- Identifies a **group of peers** and future collaborators
- Improves clinical and academic **acumen**
- **Elevates** personal clinical research goals
- Creates a **positive impact** on personal health care delivery

www.cancer.gov **www.cancer.gov/espanol**