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Continuing to Broaden Eligibility Criteria to Make Clinical Trials More Representative and Inclusive

Joint Recommendations of the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*)

February 2021

Project background

- October 2017: Joint Research Statement and multi-stakeholder work group recommendations published in *Journal of Clinical Oncology*
  - HIV/AIDS
  - Minimum age for enrollment
  - Brain metastases
  - Organ dysfunction and prior or concurrent malignancies
- September 2018: Revised NCI CTEP Generic Protocol Template reflecting ASCO-*Friends* recommendations released
- July 2020: FDA Guidance for Industry documents that align with ASCO-*Friends* recommendations finalized

A new cancer clinical trial paradigm

- Patients are eligible for a trial by default and excluded only when there is scientific rationale and/or evidence demonstrating that enrollment would compromise the patient's safety.
- In all cases, protocol development begins with informed consent as the only eligibility criteria. Any inclusion/exclusion criteria are tailored to the scientific objectives of the study, based on the investigational treatment and study population, and address only substantiated participant risks.
- Trial participants more closely resemble the population intended to receive the therapy and no group is excluded without scientific justification based on current evidence.

2021 Recommendations

Topics addressed:

- Washout periods
- Concomitant medication exclusions
- Prior therapies
- Laboratory reference ranges and test intervals
- Performance status

Multi-stakeholder work groups included:

FDA and NCI representatives, academic and community researchers, patient advocates, industry sponsors, and others

Washout Period recommendations

1. Time-based washout periods should be removed from protocol eligibility criteria in most cases. Any inclusion of time-based washout periods should be scientifically justified and clearly specified.
2. Relevant clinical and laboratory parameters should be used in place of time-based washout periods to address safety considerations.
3. Potential trial participants should have recovered from clinically significant adverse events of their most recent therapy/intervention prior to enrollment.

Concomitant Medication recommendations

1. Concomitant medications use should only exclude patients from trial participation when clinically relevant known or predicted drug-drug interactions or potential overlapping toxicities will impact safety or efficacy.

Prior Therapy recommendations

1. Patients are eligible for clinical trials regardless of the number or type of prior therapies and without a requirement to have received a specific therapy prior to enrollment unless a scientific or clinically based rationale is provided as justification.
2. Prior therapy (either limits on the number and type of prior therapies or requirements for specific therapies before enrollment) could be used to determine eligibility in the following cases:
   a) If the agents being studied target a specific mechanism or pathway that could potentially interact with a prior therapy.
   b) If the study design requires that all patients begin protocol-specified treatment at the same point in the disease trajectory.
   c) In randomized clinical studies, if the therapy in the control arm is not appropriate for the patient due to previous therapies received.
3. Trial designers should consider conducting evaluation separately from the primary endpoint analysis for participants who have received prior therapies.

Laboratory Reference Range and Test Interval recommendations

1. Laboratory test results should only be used as exclusion criteria when scientifically justified and when abnormal test results confer safety concerns.
2. Laboratory reference values should account for potential normal variations due to race, ethnicity, age, sex, and gender identity (i.e., due to surgical and/or hormonal changes).

Laboratory Reference Range and Test Interval recommendations, cont.

3. Routine re-assessment of laboratory test-based exclusion criteria should be conducted during the course of clinical research and drug development as investigational agents progress from earlier to later phase clinical trials.
4. Increasing the intervals between protocol-specified tests should be considered to help reduce patient burden and increase ability to rely on routine clinical testing, especially in later cycles of treatment and over the evolution of the protocol from earlier to later phase clinical trials.

Performance Status recommendations

1. Patients with reduced PS (e.g., ECOG PS2) should be included unless there is a scientific and/or clinical rationale for exclusion justified by established safety considerations.
   a) ECOG PS eligibility criteria should be based on the patient population in which the intervention is expected to be used in clinical practice.
   b) PS eligibility criteria should be continually re-evaluated and modified throughout the clinical development process to reflect accumulated safety data of the investigational treatment. Decisions about PS eligibility criteria should be based on early clinical safety and efficacy data about the specific investigational agent or based on known data from other drugs in the same class with similar mechanism of action. Later phase trials (e.g. phase II/III) should generally mirror the intended use population and ECOG PS2 patients should be included, unless safety concerns have manifested in earlier phase trials. The rationale for exclusion should be justified and stated explicitly.
   c) Incorporating the rationale for inclusion of a broader population into the protocol could help encourage investigators to enroll these patients.
   d) Performance status data should still be collected for use as a stratification factor, regardless of how it is incorporated into eligibility criteria.

Performance Status recommendations, cont.

3. Consider alternate trial designs, such as pre-specified cohorts with lower PS that are exempt from the primary analysis, to encourage inclusion of these patients. These cohorts would generally be small in size and exploratory in nature and could be enrolled in an incremental way to enable an early stopping rule based upon safety data. Consideration of the data analysis approach for the broader eligibility cohort and subgroup analysis should be determined during the study design phase. Early discussion with FDA about enrollment of a broader population may have implications for marketing and post-marketing research requirements.
4. Additional assessments of functional status should be considered to better characterize the functional status of ECOG PS2 patients and patients aged ≥65, such as Activities of Daily Living (ADLs) and Instrumental ADLs.