November 14
2019

Research Advocacy Network
Advancing Patient-Focused Research

Precision Medicine
Clinical Trials in Oncology

Broadening Eligibility For Cancer Clinical Trials

1

Funding
Acknowledgment

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Gratefully acknowledge funding from ECOG-ACRIN Medical Research Foundation for supporting this initiative

2

Precision Medicine in Oncology Advocate Think Tank

Category	Issue	Think Tank Solution
Communications	Awareness that not all results will have actionable mutations	Informed consent documents include a checklist to assure communication points. Consider different media to deliver.
Communications	Inconsistent language and terms used by the healthcare team	Work toward a more consistent language between health care team. Provide a glossary.
Logistical Issues	Access to tumor profiling	Educate patients about tumor profiling Provide materials to physicians that is patient friendly
Logistical Issues	Site resources	Examine cost barriers and look at ways to address – foundation or alternate funding? Patient consent to use the tissue for research
Clinical trial design issues	Narrow eligibility requirements that may preclude those with actionable mutations	Advocates in NCTN groups question each concept/protocol for eligibility requirements
Clinical trial design issues	Small size of precision medicine trials does not result in strong evidence to change clinical practice	Explore and evaluate endpoints for statistical significance and meaningfulness to patients.

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Precision Medicine Clinical Trials in Oncology SYMPOSIUM November 8-10, 2017 Grand Hyatt DFW

3

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Andrea Denicoff, RN, MS, ANP

- **Head, NCTN Clinical Trials Operations**
- **Scientific Liaison, Patient Reported Outcomes (PROs)**

4

Broadening Eligibility Criteria to Reduce Clinical Trials Barriers

Andrea Denicoff, MS, RN
Head, NCTN Clinical Trial Operations
Cancer Therapy Evaluation Program (CTEP)

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5

Improving Eligibility in Clinical Trials in NCI's National Clinical Trials Network (NCTN)

- 1996 JCO George SL : Reducing patient eligibility criteria in cancer clinical trials
- All eligibility criteria evaluated using three principles
  - Criteria should be absolutely required for anticipated scientific inference and patient safety.
  - Criteria should be unambiguously defined and capable of verification at time of audit
  - Criteria should not be regulatory, legal, or other requirement
- CALGB/Alliance studies incorporate "on-study guidelines" in phase 3 cancer treatment trials
  - Guidelines are not exclusion criteria and allows for physician judgment to prevail

6

ECOG Lung Cancer Trial Analysis: Implications

- ECOG/ACRIN Stage 4 NSCLC protocols
  - Original exclusion – " No prior cancers within 5 years"
  - Current exclusion – " No clinically active cancer"
- ALCHEMIST trial: A151216 (stage 1-3 resected NSCLC)
  - Original protocol exclusion 11/26/2013 – "No prior or concurrent cancer with 5 years"
  - Modified exclusion in amendment approved 6/8/2017 –
    - "No locally advanced or metastatic cancer requiring systemic therapy within 5 years prior to registration.
    - "No secondary primary lung cancer diagnosed concurrently or within 2 year prior to registration."

2014 JNCI Gerber et al: Estimated up to 18% of patients are excluded from lung cancer trials due to a history of a prior cancer among 210,509 patients in SEER-Medicare data

7

FDA Commentary on Eligibility Criteria: Balancing Patient Protection and Participation

- 2017 NEJM Perspective by Beaver, Ison and Pazdur:
- "….. too frequently, eligibility criteria are simply duplicated from protocol to protocol without due consideration of differing drug classes or patient populations; investigators thus lack a sound clinical rationale for excluding certain patients."
- "Unnecessarily restrictive inclusion and exclusion criteria limit accrual and access to trials and result in studies that fail to capture the heterogeneity of the patient population that will use the drug after approval."
- "Although the primary objective of eligibility criteria has been protecting patients, rational reconsideration of these criteria may lead to a more accurate description of a drug's safety and efficacy in the patients who will ultimately receive the drug — and could expedite the development of prescribing information while maintaining safety."

8

Broadening Eligibility Criteria to Make Clinical Trials More Representative

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

Manuscripts published as *Journal of Clinical Oncology* Special Series.
October 2, 2017 at ascopubs.org/journal/jco

9

ASCO-Friends Project Overview

- Prioritized assessment of specific eligibility criteria in 4 major areas:
  1. HIV/AIDS
  2. Brain Metastases
  3. Minimum Age
  4. Organ Dysfunction, Co-morbidities, Prior and Concurrent Malignancies
- Formed multi-stakeholder working groups including:
  - Patient advocates
  - Clinical investigators
  - FDA medical reviewers
  - NCI medical officers
  - Drug and biotech manufacturers
  - Pharmacologists
  - Biostatisticians

10

ASCO-Friends HIV/AIDS Criteria Recommendations

- Cancer patients with HIV infection who are healthy and low-risk for AIDS-related outcomes should be included
- HIV-related eligibility criteria should be straight-forward and focus on:
  - Current and past CD4 and T-cell counts
  - History (if any) of AIDS-defining conditions
  - Status of HIV treatment
- Treated using the same standards as other patients with co-morbidities, and anti-retroviral therapy should be considered a concomitant medication
  - http://ascopubs.org/doi/abs/10.1200/JCO.2017.73.7338

11

ASCO-Friends Brain Metastases Recommendations

- Patients with treated and/or stable brain metastases:
  - Stable = no progression for at least 4 weeks after local therapy
  - Routinely include in all phases, except where compelling rationale
- Patients with active (untreated or progressive) brain metastases:
  - No automatic exclusion
  - A one-size-fits-all approach is not appropriate. Factors such as history of the disease, trial phase and design, and the drug mechanism and potential for CNS interaction should determine eligibility.
- Patients with leptomeningeal disease:
  - In most trials, exclude, although there may be situations that warrant a cohort of such patients in early phase trials

12

Background: Minimum Age Recommendations

- Children and adolescents < 18 years of age have traditionally been excluded from clinical trials with novel agents until extensive data are available from adults (years after the approval of an agent)
- Historically, concern that a high-profile AE could endanger the whole drug development program
- No evidence to support this based on FDA review of successful and failed development of oncology drugs
- Drug exposure for adolescents 12- 18 years of age is similar to adults

13

13

ASCO-Friends Minimum Age Recommendations

- Initial dose-finding trials:
  - Pediatric-specific cohorts should be included when there is strong scientific rationale (based on molecular pathways or histology and preclinical data)
- Later-phase trials:
  - Trials in diseases and therapeutic targets that span adult and pediatric populations should include pediatric patients with the specific disease under study
  - Patients aged 12 years and above should be enrolled in such trials
  - Patients under 12 years may also be appropriate

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14

14

ASCO-Friends Organ Dysfunction Recommendations

- Informed by an analysis of Kaiser dataset of 13,000 patients newly diagnosed in 2013-2014
- Renal function should be based on creatinine clearance (calculated by Cockcroft-Gault or MDRD)
  - Liberal creatinine clearance (e.g., >30 mL/min) should be applied when renal excretion not significant
  - Follow established dose modification strategies.
- Hepatic Function
  - Current tests are inadequate, particularly drug metabolism capability
  - Employ standard clinical assessments relative to institutional normal ranges

15

ASCO-Friends Prior and Concurrent Malignancies Recommendations and Cardiac Testing

- Prior Malignancy
  - Patients eligible if prior therapy at least 2 years prior and no evidence of disease
- Concurrent Malignancy
  - Patients eligible if clinically stable and not requiring tumor-directed therapy
- Cardiac testing
  - If no known cardiac risks, ejection fraction tests should not be exclusionary
  - Investigator assessment with a validated clinical classification system
  - If no cardiac risks, ECG should be eliminated in later phases

16

Implementation in CTEP Network Clinical Trials

- ETCTN: Early Therapeutics Clinical Trials Network
  - Incorporate ASCO-Friends recommendations in new centralized protocol authoring with eligibility criteria as part of protocol template
  - Collaborate with NCI's Clinical Trials Reporting Program (CTRP) to structure eligibility to improve downstream impact on trial searching
  - Collaborate with Theradex for harmonizing data elements in Rave associated with eligibility criteria
- NCTN: NCI National Clinical Trials Network
  - NCTN Groups - continue to expand use of broadened eligibility criteria across disease and scientific committees
  - Network Accrual Core Team (ACT) Eligibility Task Force - Network Operations Leaders, Site Investigators, Research Coordinators and Patient Advocates involved in dissemination

Broadening Eligibility: Challenges to Implementation

- Trial collaborations with industry will require discussions to balance safety and overly strict exclusion criteria
  - FDA's role will be important
- CTEP reviewers will need to review criteria in protocols for compliance to template criteria when finally agreed upon
- PIs and study teams will need to remain committed to considering eligibility, avoid re-use of prior more restrictive criteria from older trials
- Site investigators and their research teams will need to modify site processes to identify and screen potential clinical trials participants
- To be successful, it will require increased awareness and commitment to broaden eligibility criteria across all stakeholder groups

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19

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Discussion

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20