Clinical Trial Eligibility and ASCO

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No COI
Broadening Eligibility Criteria to Make Clinical Trials More Representative

Joint Project of the American Society of Clinical Oncology and Friends of Cancer Research

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The Clinical Trial Is Open.
The Elderly Need Not Apply.
Under-Representation of Older Adults in Cancer Registration Trials: Known Problem, Little Progress

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Modernizing Eligibility Criteria for Molecularly Driven Trials


ABSTRACT

As more clinical trials of molecularly targeted agents evolve, the number of eligibility criteria seems to be increasing. The importance and utility of eligibility criteria must be considered in the context of the fundamental goal of a clinical trial: to understand the risks and benefits of a treatment in the intended-use patient population. Although eligibility criteria are necessary to define the population under study and conduct trials safely, excessive requirements may severely restrict the population available for study, and often, this population is not reflective of the general population for which the drug would be prescribed. The American Society of Clinical Oncology Cancer Research Committee, which comprises academic faculty, industry representatives, and patient advocates, evaluated this issue. Evaluation results were mixed.
ASCO-Friends of Cancer Research
Project Overview

• Prioritized assessment of specific eligibility criteria:
  • Brain Metastases, Minimum Age, HIV/AIDS, Organ Dysfunction, and Prior and Concurrent Malignancies

• Formed multi-stakeholder working groups
  • Patient advocates
  • Clinical investigators
  • FDA medical reviewers
  • Drug and biotech manufacturers
  • Biostatisticians
  • Pharmacologists
Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group

Stuart M. Lichtman, R. Donald Harvey, Marie-Anne Damiette Smit, Akhir R. Rahmam, Michael A. Thompson, Nancy Roach, Caroline Schenkel, Susanna S. Brunsøe, Patricia Cortazar, Dana Walker, and Louis Helmbach
What is the goal?

• Raise the participation of patients in trials
• Challenge assumptions & past practice
• Create new culture – only exclude where safety warrants
  • Shape perception/attitudes/practice of clinical trial eligibility
  • Create and implement new criteria
  • Justify exclusions or differences between trial participants and overall patient population with the indicated disease
  • Active discussion during trial design and FDA pre-IND meetings
• Not just publication of recommendations, but implementation
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.
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.
HIV+ 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.
Organ Dysfunction

- Renal function
- Hepatic function
- Cardiac
- Prior malignancy
- Functional assessment
Effect of comorbidity-renal insufficiency

All patients over 65 years
Baseline creatinine clearance > 30 ml/min

Renal Dysfunction

• Dosing
  • Chemotherapy was adjusted based on calculated CrCl (methotrexate, capecitabine)

• Endpoints:
  • toxicity, dose modification, therapy completion, relapse-free survival, and overall survival.
Renal Dysfunction

• Patients with renal insufficiency who received dose modifications were not at increased risk for complications compared with those who did not have renal insufficiency and received a full dose; efficacy was maintained.

• Excluding from clinical trials patients with renal insufficiency but good performance status on the basis of concern of excessive hematologic toxicity or poor outcomes may not be justified with appropriate dosing modifications.

• Results should be considered in the design of clinical trials for older patients.
Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group

Stuart M. Lichtman, R. Donald Harvey, Marie-Anne Damiette Smit, Atiqur Rahman, Michael A. Thompson, Nancy Roach, Caroline Schenkel, Suanna S. Bruinooge, Patricia Cortazar, Dana Walker, and Louis Fehrenbacher

## Kaiser Permanente Northern California
2013-2014 (n=13,000)
Lowest GFR (cc/min) at Cancer Diagnosis

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>&lt;30 cc</th>
<th>30-39cc</th>
<th>40-49cc</th>
<th>50-59cc</th>
<th>30-59cc</th>
<th>&lt;60 cc</th>
<th>60+ cc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (%)</td>
<td>1.4</td>
<td>2.3</td>
<td>5.9</td>
<td>10.7</td>
<td>18.9</td>
<td>20.3</td>
<td>79.7</td>
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<tr>
<td>Colorectal (%)</td>
<td>2.4</td>
<td>4.0</td>
<td>6.9</td>
<td>11.3</td>
<td>22.2</td>
<td>24.6</td>
<td>75.4</td>
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<tr>
<td>Lung (%)</td>
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<td>4.7</td>
<td>9.0</td>
<td>11.4</td>
<td>25.1</td>
<td>27.7</td>
<td>72.3</td>
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<tr>
<td>Bladder (%)</td>
<td>9.1</td>
<td>9.5</td>
<td>10.9</td>
<td>16.3</td>
<td>36.7</td>
<td>45.9</td>
<td>54.1</td>
</tr>
</tbody>
</table>

Data: Fehrenbacher, personal
Renal Function

- CrCl rather than serum creatinine concentrations.
- Inclusion of patients with renal dysfunction could be liberalized in specific settings.
- If renal toxicity and clearance are not of concern, then lower CrCl values of >30 mL/min should be used for inclusion.
  - When published dose modifications allow for safe and effective administration of the drug and are not likely to change outcomes (e.g. carboplatin, methotrexate, capecitabine).
  - When the totality of the available nonclinical and clinical data, including PK and PD data, indicates that inclusion of patients with renal dysfunction is safe.
Organ Dysfunction

Recommendations

• 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
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
ASCO Current Eligibility Projects

- Performance status
- Washout Periods and Concomitant Medications
- Prior therapies
- Test Intervals and Lab Reference Ranges
Conclusion

• Overall clinical trial participation is poor
• Patients over 70 years of age are particularly under represented
• Clinical trials need to be designed so that results reflect the patients with the disease
• We all want to practice evidence based oncology; cannot do that in older patients due to the lack of that evidence
• Older patients are the majority of cancer patients and have the majority of cancer mortality
• Please design trials with their needs in mind
Inclusivity Conclusions

• Starts with clinical trial design
• Eligibility should be in line with the goal of the trial and the patients to be accrued
• Need to make trial results more in line with the ‘real world’
• Need buy-in from the various stakeholders particularly pharma
• Need to seek out patients from under represented groups
  • Minorities
  • The elderly
• Moving away from traditional chemotherapy will force new thinking in this area
Thank you