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Organ function criteria expansion

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Broadening Eligibility Criteria to Make Clinical Trials More Representative

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SPECIAL ARTICLE

Modernizing Eligibility Criteria for Molecularly Driven Trials

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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.

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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

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What is the goal?

- **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 <u>implementation</u>**

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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.

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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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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 CD_4 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.

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Organ Dysfunction Recommendations

- Informed by an analysis of Kaiser dataset of 13,000 newly diagnosed patients in 2013-2014.

Table 2. Kaiser Permanente Northern California 2013 to 2014: Lowest Glomerular Filtration Rate at Cancer Diagnosis

	% of Patients (N = 13,000)						
Cancer Site	< 30 mL/min	30-39 mL/min	40-49 mL/min	50-59 mL/min	30-59 mL/min	< 60 mL/min	≥ 60 mL/min
Breast	1.4	2.3	5.9	10.7	18.9	20.3	79.7
Colorectal	2.4	4.0	6.9	11.3	22.2	24.6	75.4
Lung	2.6	4.7	9.0	11.4	25.1	27.7	72.3
Bladder	9.1	9.5	10.9	16.3	36.7	45.9	54.1

NOTE. Calculated using Cockcroft-Gault equation.

Lichtman SM, Harvey RD, Smit M-A D, et al. J Clin Oncol 2017;33:3753-3759.

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

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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

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Thank you