

Designing Clinical Trials for Real World Patients:

Recommendations from the CARG/NIA/NCI U13 Conferences

Supriya Mohile, MD, MS
Director, Geriatric Oncology
University of Rochester

Designing Therapeutic Clinical Trials for Older and Frail Adults With Cancer: U13 Conference Recommendations

Arti Hurria, William Dale, Margaret Mooney, Julia H. Rowland, Karla V. Ballman, Harvey J. Cohen, Hyman B. Muss, Richard L. Schilsky, Betty Ferrell, Martine Extermann, Kenneth E. Schmader, and Supriya G. Mohile

Goals:

1. Identify gaps in knowledge of cancer therapy in older adults
2. Study design of therapeutic clinical trials
3. Methods to optimize patient accrual
4. Propose opportunities for multidisciplinary studies
5. Disseminate

Gaps-Clinical Trial Design is Inadequate for Older Patients

Eligibility and Patient Selection

Very old, organ dysfunction, comorbidity, cognitive impairment, functional impairment, prior malignancy

Pharmacology

Complicated schemes and sampling strategies,
effects altered by age and comorbidity

Toxicity assessment

Do not include impact on function, cognition,
or other sequelae important to older adults

Endpoints

Survival and response vs
functional benefit and quality of life improvement

Survival by Geriatric Assessment Status in Older Patients with DLBCL

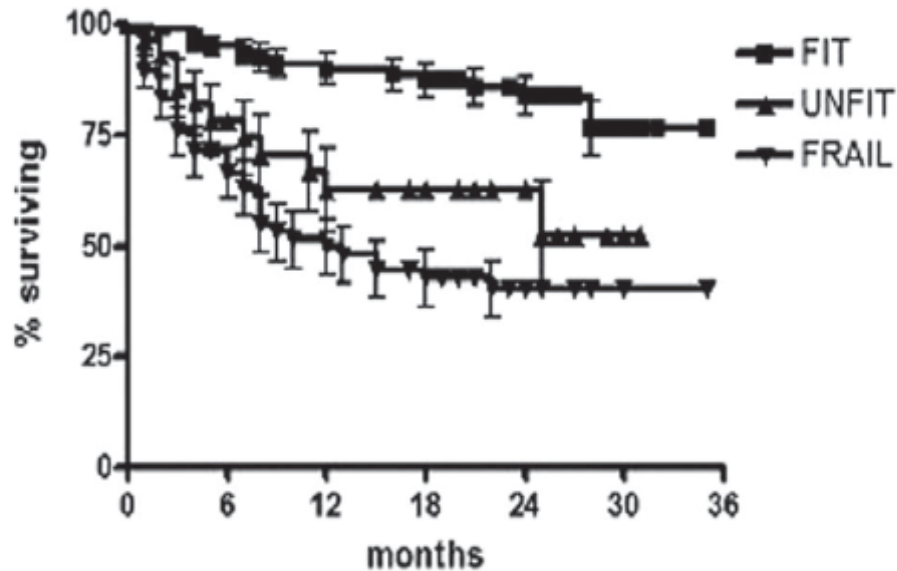
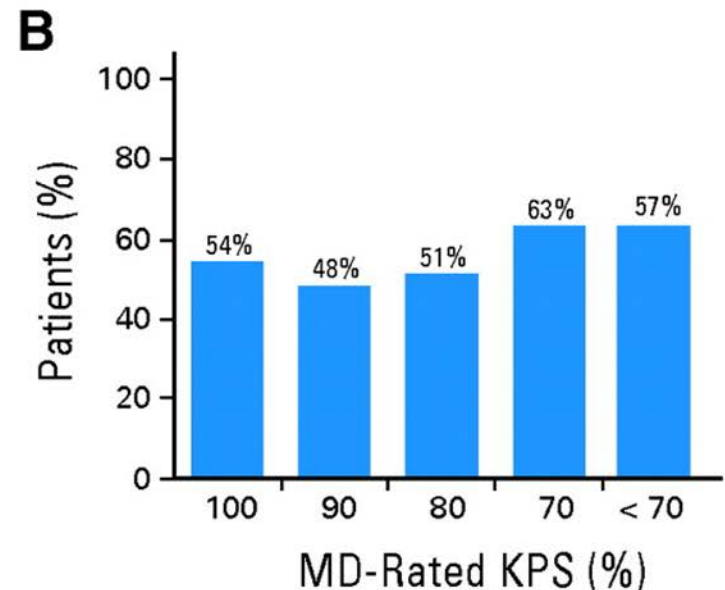
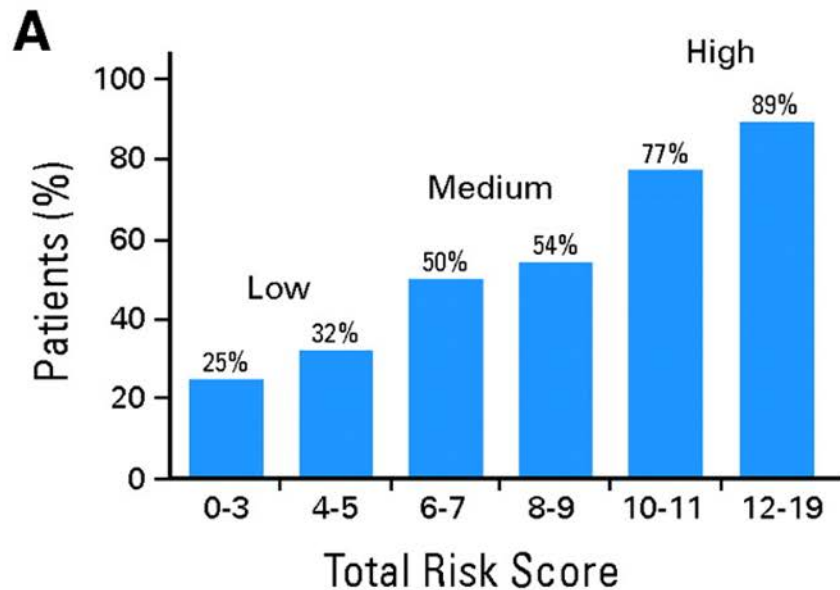


Figure 1. Actuarial overall survival curves of elderly patients with DLBCL classified as “fit,” “unfit” and “frail” according to CGA, independent of treatment received.

-In multivariate analysis, GA status was associated with survival

-treatment intensity and curative vs palliative tx approach were not associated with OS

GA Measures Perform Better than Oncology PS for Assessing Older Adults



GA is crucial for “real-world” older patients with cancer

- **1: GA captures clinically important issues that otherwise go undetected**
- **2: GA is feasible to conduct in clinical practice and clinical trials**
- **3: GA variables can identify older adults who at are high risk for adverse outcomes from cancer treatment**
- **4: GA can help guide decision-making and interventions to improve outcomes for older patients with their cancer and their caregivers**

Dale, , et

ASCO guidelines framework (in progress);

Mohile, Hurria, Dale et al.

Questions for Older Adults with Cancer

- Established regimens
 - How tolerable are established treatment regimens in older/frail patients?
 - Are established treatment regimens efficacious in older/frail patients?
 - How (and/or should) existing regimens be modified for older/frail patients?
- New regimens
 - Should new agents/regimens be evaluated in the older/frail patients? If so, how?
 - Should regimens be considered only for older/frail patients?

Randomized Controlled Trials

Description	Potential Objectives	Advantages	Limitations	Examples
<ul style="list-style-type: none"> -Accrue only older patients -Accrue patients of all ages and then stratify into age groups representative of patients with disease 	<ul style="list-style-type: none"> -Determines gold standard of treatment through comparisons of efficacy and tolerability -Develop novel end points such as composite measures of tolerability/toxicity 	<ul style="list-style-type: none"> -Studies of older patients are important since they are often excluded from clinical trials -Endpoints can be tailored for geriatric oncology patients 	<ul style="list-style-type: none"> -Large sample sizes often required -Accrual may be slower due to need to enroll patients in specific age strata -Trials for all patients may not include appropriate endpoints for older adults 	<ul style="list-style-type: none"> -CALGB 49907 Muss et al.; NEJM 2009—evaluated different adjuvant chemotherapy options for older patients with early stage breast cancer -FOCUS-2 Seymour et al.; Lancet 2011—established first line treatment options for older patients with advanced colorectal cancer

Prospective Cohort Study

Description	Potential Objectives	Advantages	Limitations	Examples
<ul style="list-style-type: none"> -Assessment of treatments to evaluate outcomes of interest in older patients -Cohort can be defined by host, tumor, or treatment factors -Observational, hypothesis-driven 	<ul style="list-style-type: none"> -Determine patterns of care -Understand decision-making -Determine toxicity and feasibility of specific therapies 	<ul style="list-style-type: none"> -Easier to design and implement -Enrollment of patients receiving standard of care treatments increases generalizability 	<ul style="list-style-type: none"> -Not randomized -Can still require significant resources to accurately capture dosing and toxicity 	<ul style="list-style-type: none"> -CALGB 369901 Mendelblatt et al. JCO; 2010— Evaluated patient preference as a determinant for use of adjuvant chemotherapy -Italian Lymphoma Group; Tucci et al.; Leuk/Lymphoma 2015- GA frailty variables and patterns of care in older patients with DLBCL

Embedded Study

Description	Potential Objectives	Advantages	Limitations	Examples
<p>-Assessment of correlatives</p> <p>-Additional measures of interest (such as GA measures) are placed within infrastructure of parent study</p>	<p>-Use of GA to describe cohort</p> <p>-Use of GA in longitudinal follow-up to understand function/QoL endpoints</p> <p>-Identify which patients are at highest risk for adverse outcomes (e.g., toxicity)</p>	<p>-Better characterization of geriatric oncology population that enters the study</p> <p>-Better identification of baseline predictors of treatment tolerance and longitudinal declines in function</p>	<p>-Parent study may not be specifically targeted to older patients, limiting sample size</p> <p>-Optional participation in embedded study may affect generalizability</p>	<p>-CALGB 361006 PI: Klepin; GA embedded in CALGB 11001</p>

Single-arm Trial

Description	Potential Objectives	Advantages	Limitations	Examples
<p>-Current design for most phase II clinical trials</p> <p>-No randomization</p> <p>-All patients receive study-defined treatment</p>	<p>-Evaluate efficacy of drug for which there are limited data in older adults</p> <p>-Identify which patients are at highest risk for adverse outcomes (e.g., toxicity)</p> <p>-Understand age-related changes in pharmacokinetics /dynamics</p>	<p>-Quantify novel end points such as impact of therapy on function and QoL</p> <p>-Fill in gaps in knowledge regarding efficacy, feasibility, toxicity of drugs that have been understudied in older adults</p>	<p>-No randomization or comparison of treatments</p>	<p>-CALGB 9762 Lichtman et al.; JCO, 2006— Prospective evaluation of relationship between patient age and paclitaxel pharmacology</p>

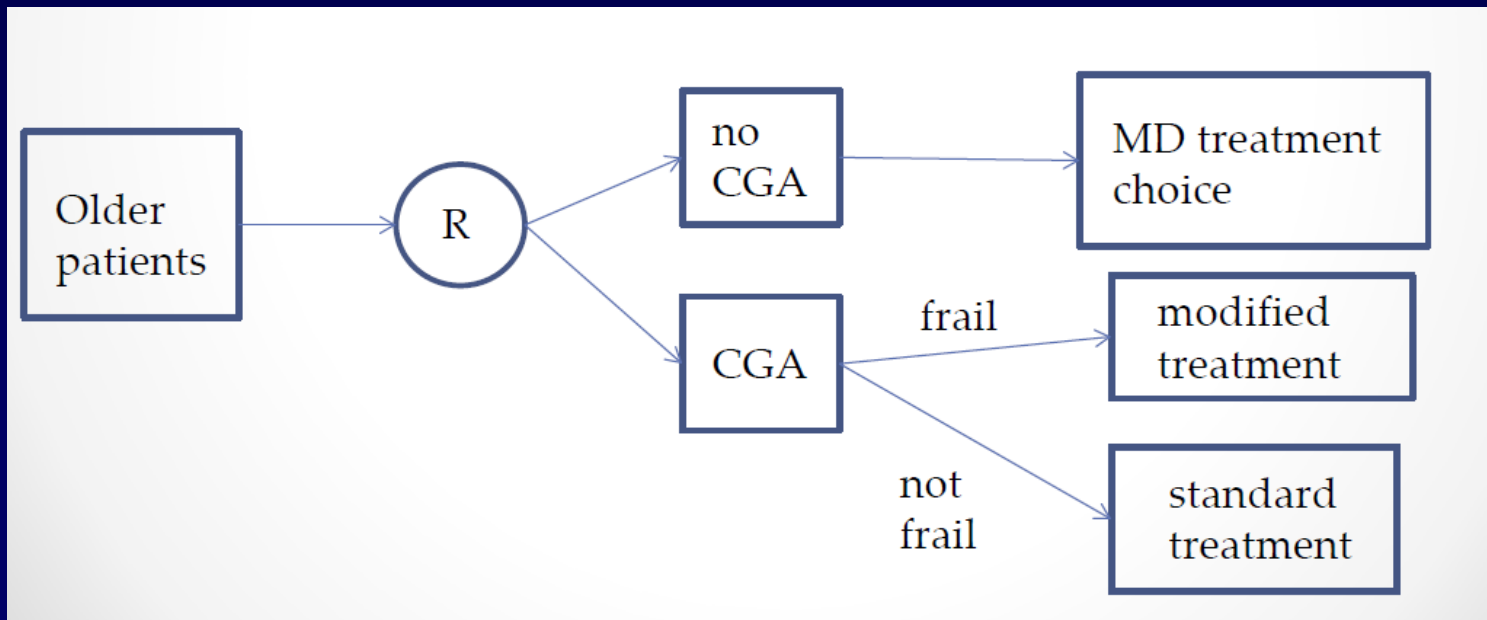
Extended Trial

Description	Potential Objectives	Advantages	Limitations	Examples
-Addition of cohort of older patients to treatment arm from RCT that was shown to be superior	-Evaluate tolerability of treatment found to be superior in older adults	-Trial infrastructure is already in place -Accrual of older adults may be easier because efficacy of treatment has been established -Additional data in older patients will be obtained	-Currently no precedent exists for reopening studies -Accrual is only to the superior arm to bolster data about tolerability; data regarding efficacy of treatment compared to inferior arm is not obtained	-No precedent

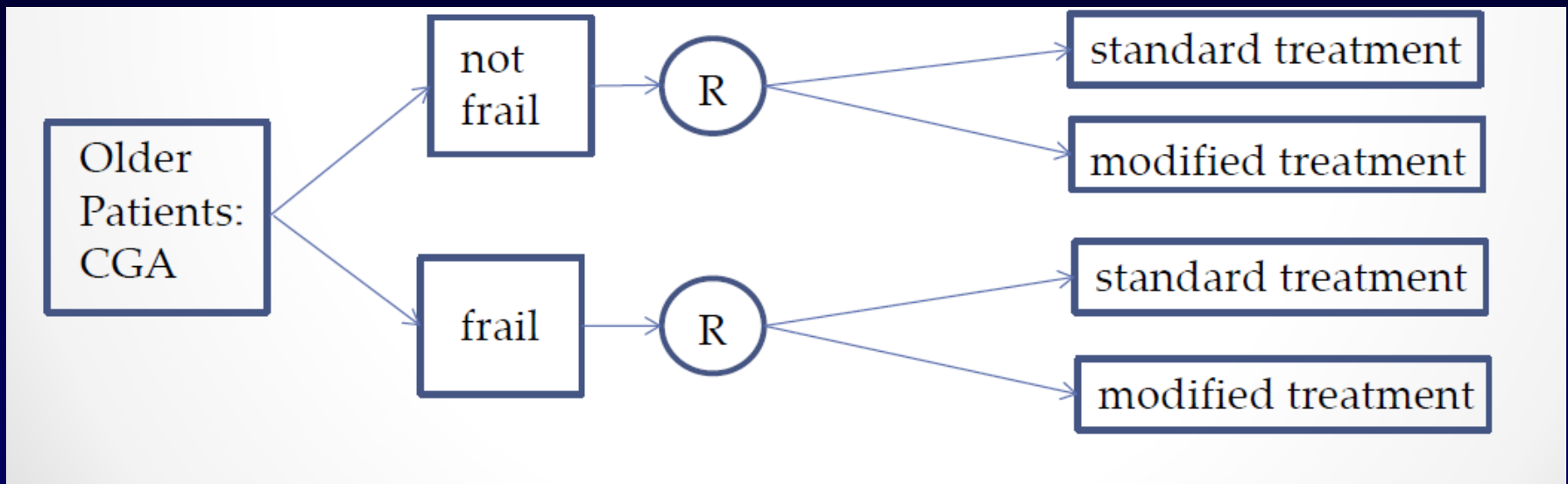
Phase III (Bio) Marker Design

-Marker-based strategy

- Patients randomized between marker assigned treatment or not
- Results in patients with same marker status receiving the same treatment so yields large trials
- ESOGIA trial for older patients with advanced lung cancer**
- Corre et al.; JCO 2016



Marker-by-Treatment Interaction Design



Sarget et al; JCO 2015 and Friedlin et al; JNCI 2010

Summary

- Study design reflects current information
 - prospective cohort
 - embedded study
 - phase II designs
 - phase III designs including extended study options
- Data is growing that now can help define eligibility for trials for older and/or frail adults
- Endpoints for studies in older/frail patients will likely differ from traditional clinical trial endpoints