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Elderly Patients and Clinical Trials

EMA Notes for Guidance

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MPA



"Selection bias" is always there

- It is not the protocol
- It is the clinician!

- Or?

- If not "cancer", why not "heart failure"
- About 80% of cases >65 years of age

Table 3. Frequencies of Exclusion Criteria That Might Negatively Affect the Inclusion of Older Individuals in Ongoing Clinical Trials Regarding Heart Failure

Exclusion Criterion	Frequency, No. (%)
Upper age limit	64 (25.5)
Reduced life expectancy	91 (36.3)
Total comorbidity	201 (80.1)
Generic	26 (10.4)
Specific	190 (75.7)
Specific disease exclusions	
Renal	100 (39.8)
Liver	54 (21.5)
Neurologic	73 (29.1)
Lung	61 (24.3)
Cancer	42 (16.7)
Psychiatric	22 (8.8)
Other	85 (33.9)
Cognitive impairment	32 (12.7)
Physical disability	35 (13.9)
Exclusion by drug treatment	47 (18.7)
Polypharmacy ^a	14 (5.6)
Specific drug treatment	46 (18.3)
Inability to attend follow-up meeting	24 (9.6)
Hearing or visual deficits	11 (4.4)
Communication barriers	5 (2.0)

^aClinical trials using general terms to exclude patients receiving drug treatment or excluding patients receiving treatment with drugs belonging to 3 or more different pharmacologic groups.

Upper age limit

65 to 95 years, median 80 years.

28.2% in the period 2002-2006 (n = 149)

21.6% in the period 2007-2008 (n = 102)

Sponsor

Public institutions 21/59 [35.6%]

Private entities 5/36 [13.9%]

Trials w. Medicinal Products by Region

European Union 16/33

United States 3/37

Guidance Documents Elderly

- Cardiac Failure 2000
 - Not discussed

General guidelines

- ICH topic E7 1994
- Questions and Answers E7 2010
- Guidance Consistency Group
 - "Refer to proper NfG" instead, as this is not unique to X
 - Probably not for "heart failure" and "elderly"

Q and A E7

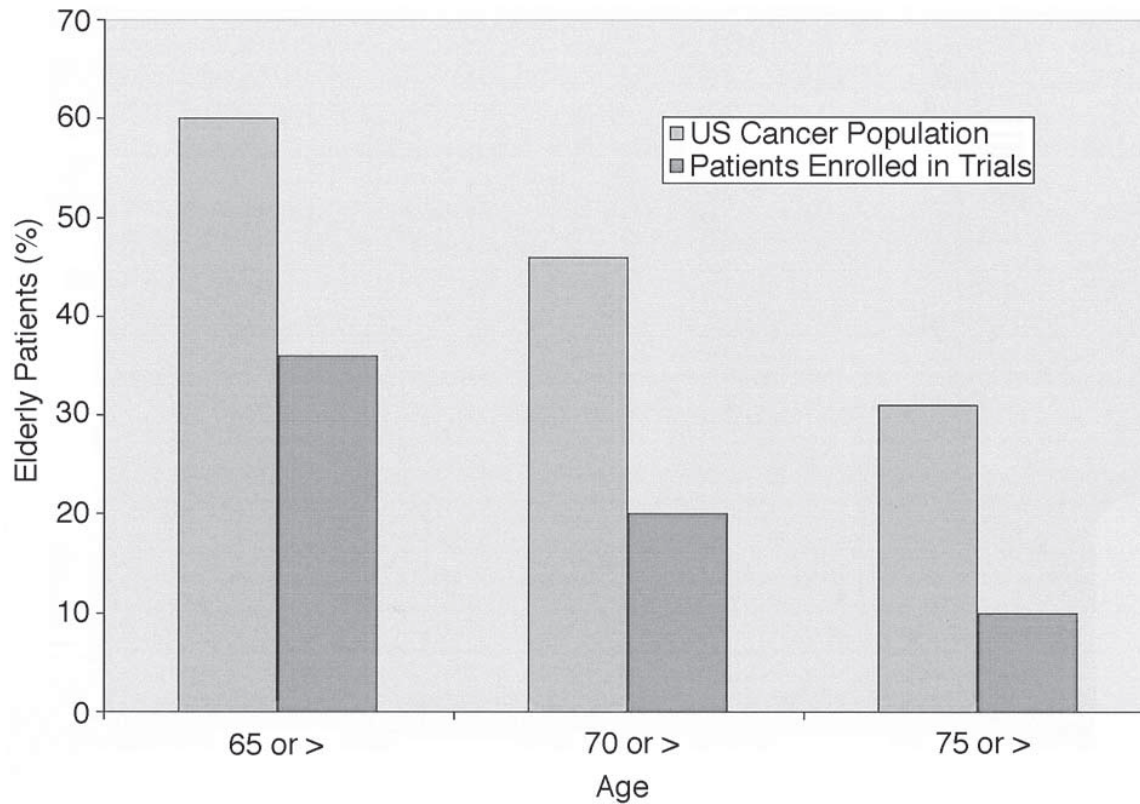
- Why?
- "Representative"
- Or at least "informative" (E7 n >100)
- Restrictions to be avoided
- *"Frail" patients randomly distributed*
- Specific safety data to look for (cognition, falls, ...)
- PK

Anti-cancer NfG

- **Elderly and frail patients (2005)**
- In many indications elderly patients represent the majority of the patient population.
- If not reasonably reflected in the data base, this should be justified.
- Some compounds may be specifically suitable for the treatment of elderly, e.g. due to PK properties such as low sensitivity to impaired organ function. In these cases, dedicated studies in the elderly are encouraged. It is acknowledged that it may be hard to identify appropriate reference therapies in some of these cases and that other outcome measures than PFS/OS might become more relevant. In these cases it is advisable to seek regulatory agreement on the development program.
- Frail patients, whether elderly or not, with clearly impaired PS constitute a vulnerable group of patients rarely included in conventional confirmatory studies. Clinical studies in this group of patients are encouraged from a regulatory perspective.



Registration Trials Cancer 1995 – 2002 (US) (JCO 2004)





Registration Trials pts >65 years of age (JCO 2004) Use in clinical practice (JCO 2010)

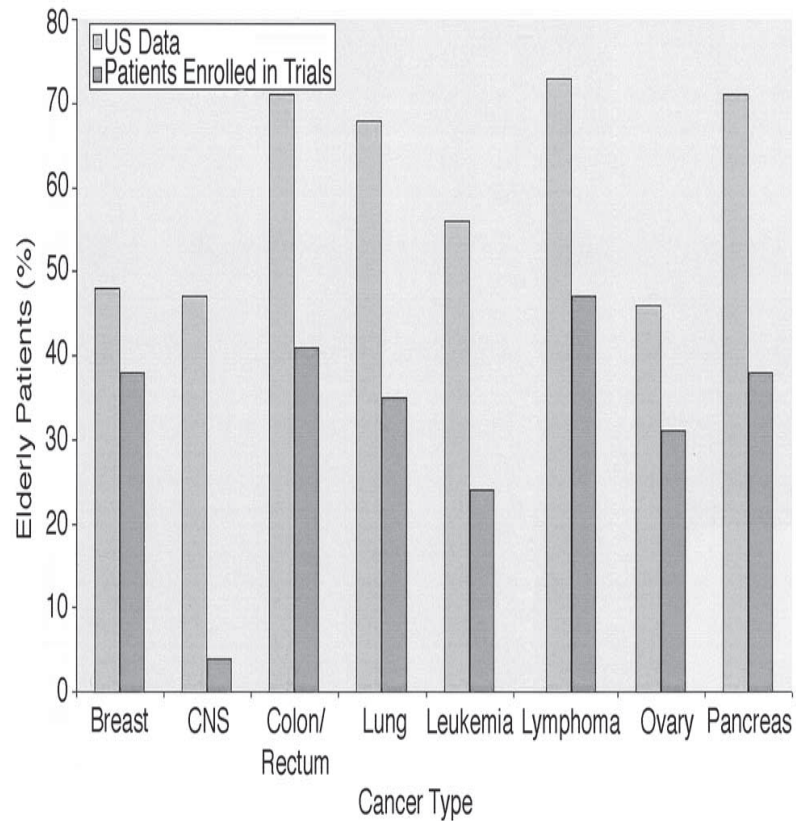


Table 2. Characteristics of Patients With Advanced Stage NSCLC Who Were Receiving Chemotherapy and Adjusted Probability of Receiving Chemotherapy in the CanCORS Study

Characteristic	Patients			
	No.	%	Adjusted %*	95% CI
Age, years†				
< 65	137	79	72	65 to 79
65-64	213	64	62	57 to 66
65-74	273	61	62	57 to 66
≥ 75	175	42	47	42 to 52

The Clinician as Gatekeeper? the FOCUS trial (MRC)

- Advanced Colorectal Cancer
- Permissive incl. criteria
- Median age 64 years in the trial
- Median age at death of CRC in the community 77
- 59 participating and responding oncologists
- Enrolled 422 pts in the FOCUS trial
- In parallel, 715 pts treated with chemotherapy off-trial
 - Lancet 2011, FOCUS2 trial

Prior to First Registration Trial

- Limited PK data
 - impaired liver/kidney function, PK interaction, food interaction, ..
- Limited tolerability and toxicity data
 - diarrhoea, dehydration, renal toxicity, cardiovascular toxicity, co-morbidity ..
- Limited activity and efficacy data
- Clinician as gatekeeper to protect the patient and the study
- **But further confirmatory studies in other indication?**

Including elderly and frail patients

- Risk to the patient
- Dose adjustments and supportive measures
 - Learning curve
 - Start with otherwise healthy patients
- Diluting the treatment effect
- Risk to the study

- Need for Risk Reduction

Risk Reduction

- Gain experience in otherwise healthy patients
- Reasonable data base: tolerability, toxicity, efficacy, PK, co-morbidity interaction, etc.
- Stratified enrolment
 - Primary efficacy/safety population: "Patients normally enrolled in clinical trials"
 - Secondary safety/efficacy population: Those excluded but normally treated in clinical practice
 - consider e.g. lower starting dose with **dose escalation** (maximum tolerated dose drugs)



Incentives

- Studies specifically designed for the frail and elderly
- Has been done in lung cancer (vinorelbine)
- Recently in colorectal cancer (FOCUS2)
- AML and the elderly? (advice procedures)

- Data protection +1 year?
- ?

Summary

- It is not about the Protocols
- It is not about the Notes for Guidance
- It is about the clinician as gatekeeper
 - protecting the patients
 - protecting the trials
- There is a need for risk reduction for patients and trials
- There is a need for incentives