VII CONVEGNO NAZIONALE DELLA
RETE ONCOLOGICA SIFaCT

Oltre il modello mutazionale e l'oncologia di precisione: la medicina personalizzata

ONCOFARMA

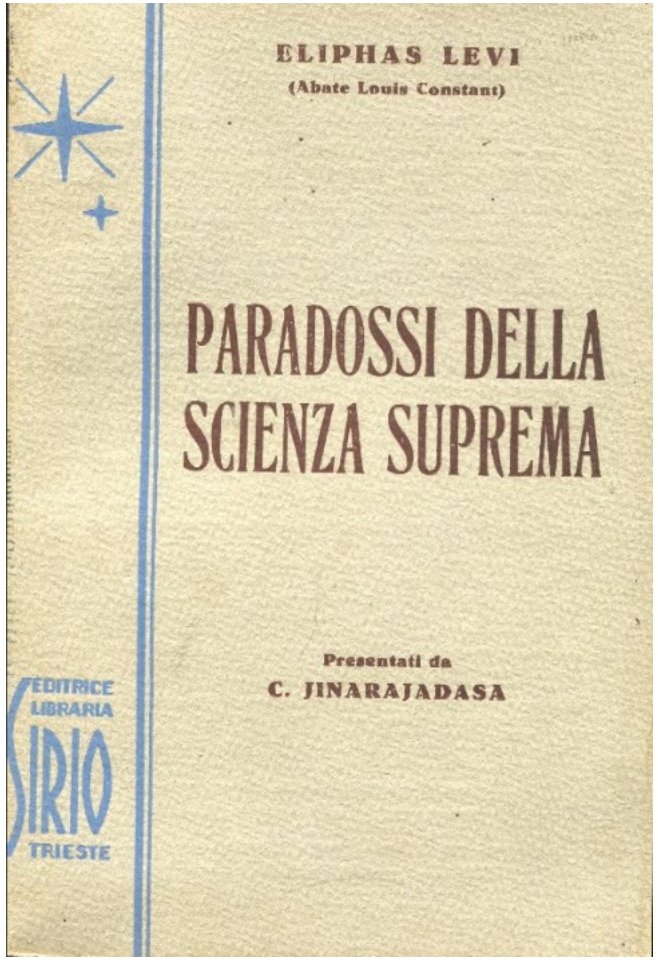
Sifact
SOCIETÀ ITALIANA DI FARMACIA CLINICA E TERAPIA

Milano 23-24 Giugno 2023

Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

Raffaele Costanzo

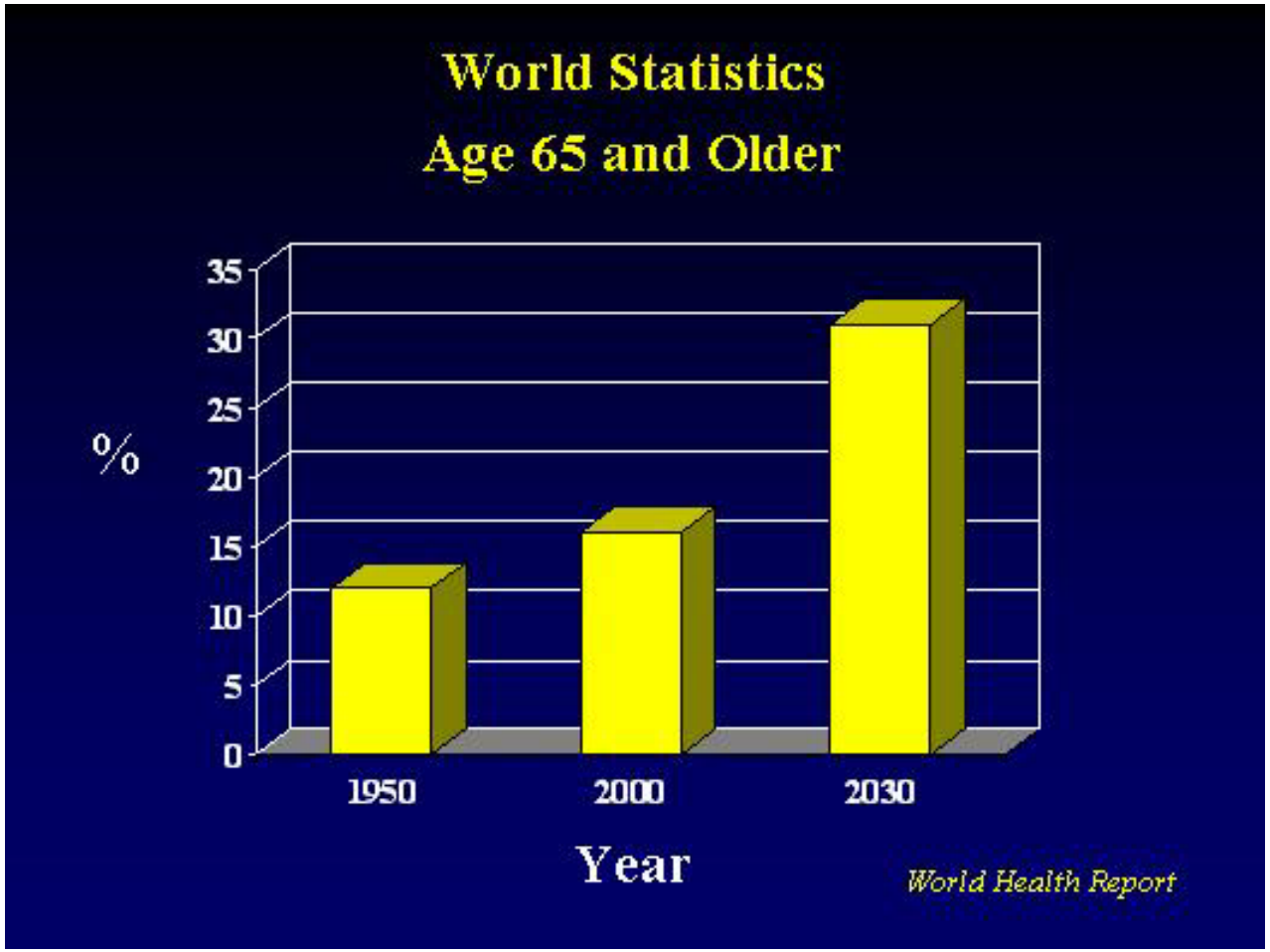
Is the elderly different from trial patients?



Is the elderly different from trial patients?

Is it a paradox?

Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

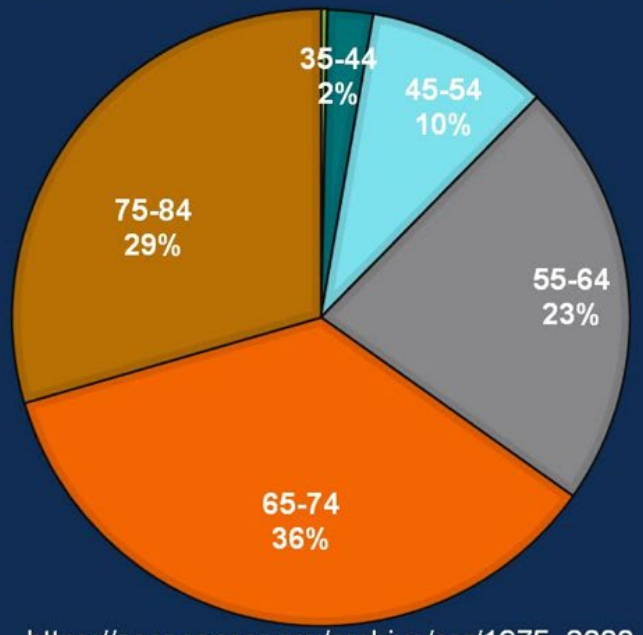


Hurria A, ASCO 2007

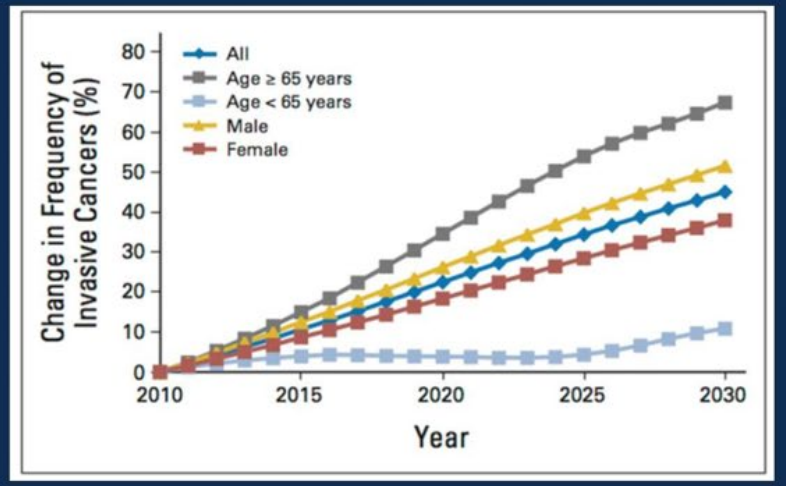
Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

Lung Cancer is Primarily a Disease of the Elderly

Age at Lung Cancer Diagnosis



https://seer.cancer.gov/archive/csr/1975_2000



Pal and Hurria, JCO 2010

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

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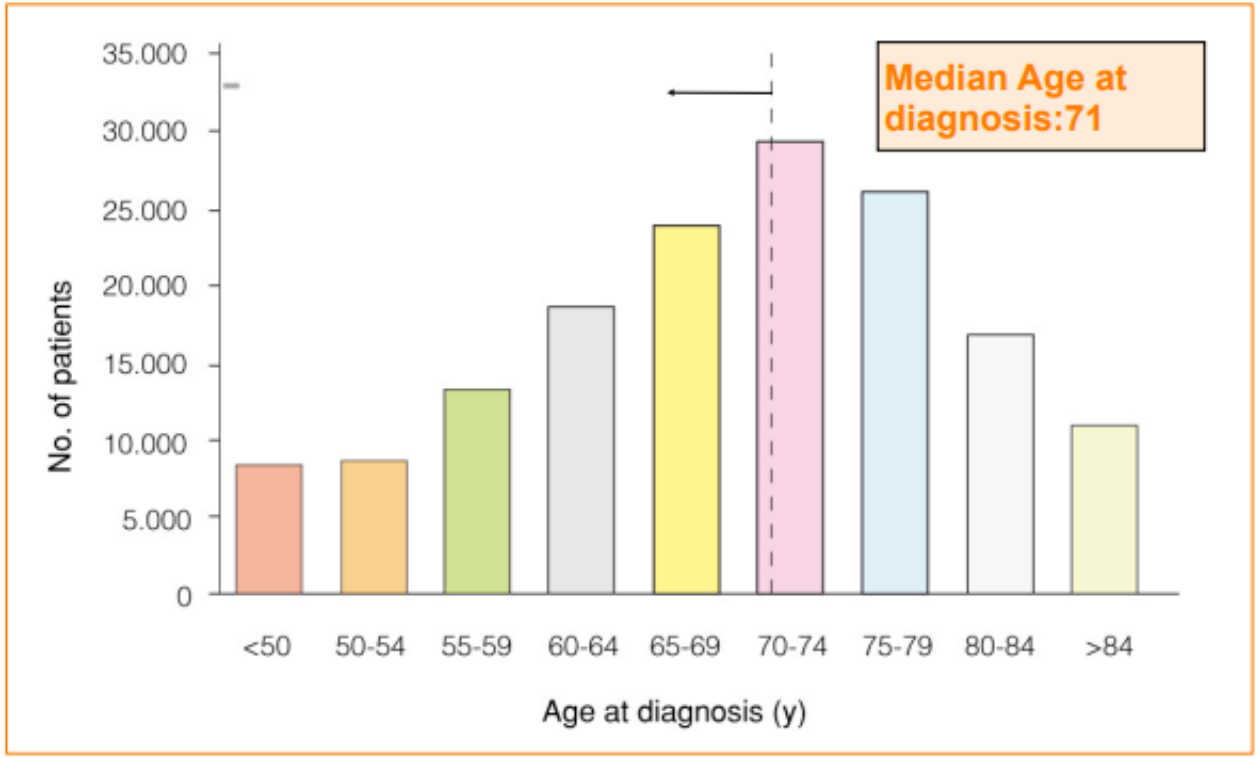
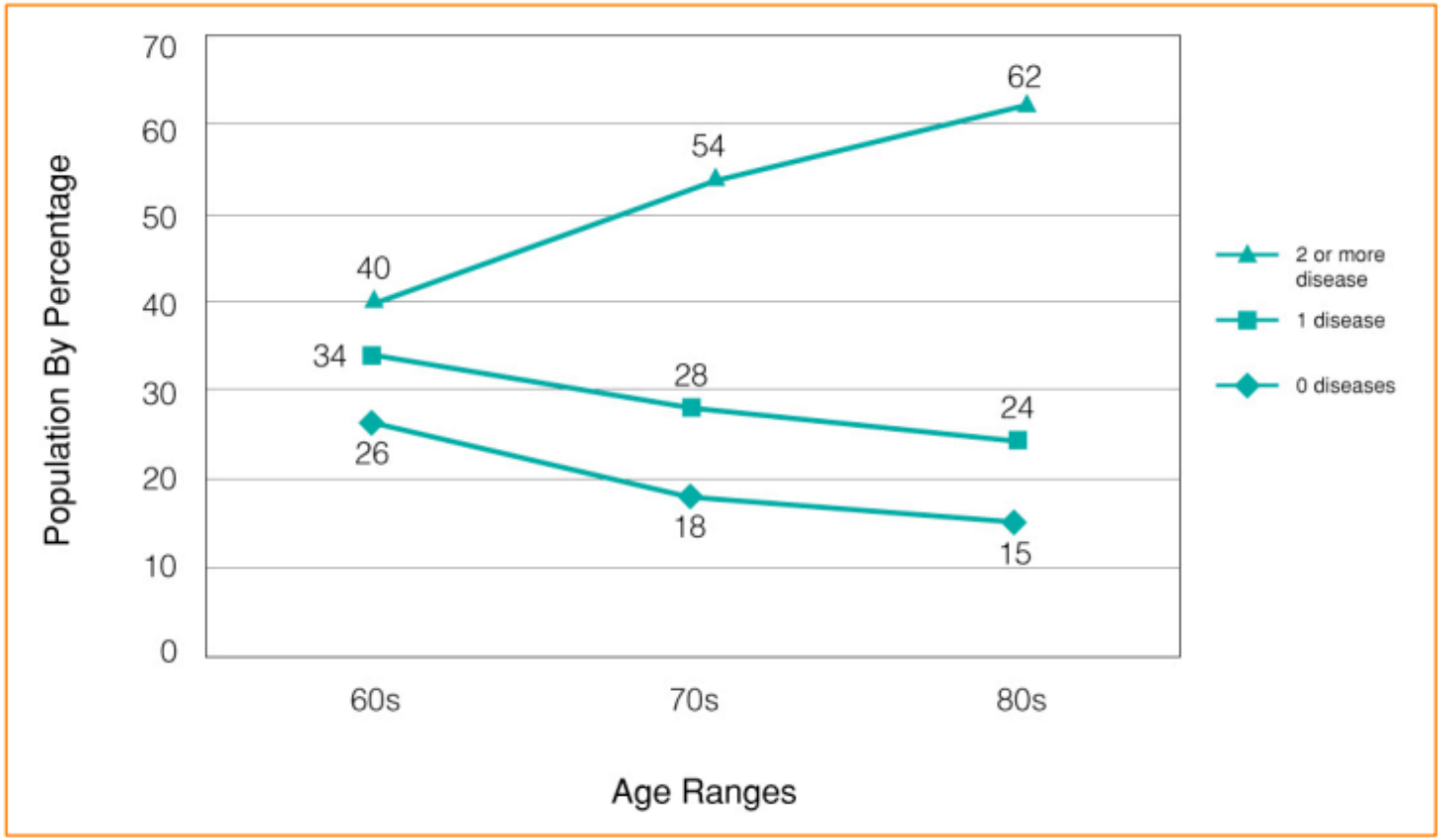
Presented by: JD Patel

US NSCLC Incidence Age at diagnosis

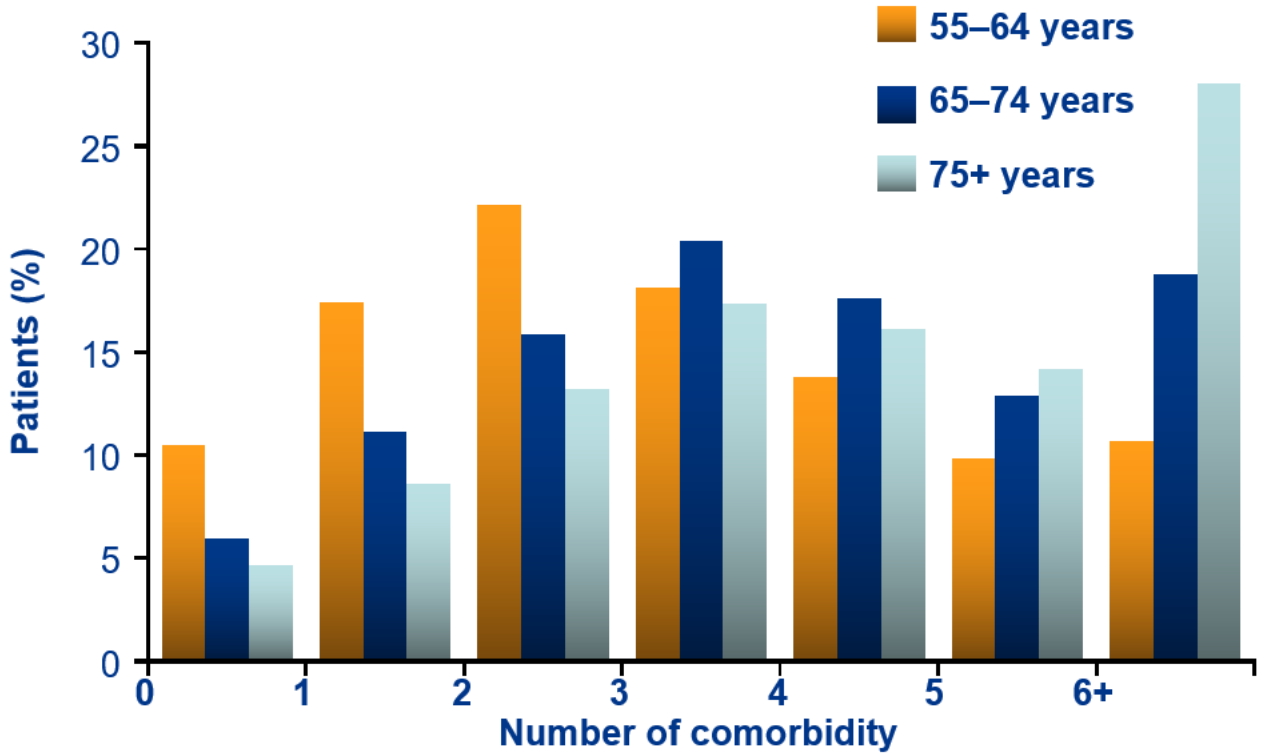


Comorbidity increases with age…



Guralnik, JM et al. "Aging in the Eighties: The prevalence of comorbidity and its association with disability". Advance Data Report 170. 1989

Standard management of elderly patients may be affected by comorbidity



Yancik R. Cancer 1997;80:1273–83

Standard management of elderly patients may be affected by organ decrease functions

- **Cardiovascular function**[1]
  - decreased elasticity of arterial system
  - loss of myocytes and atrial pacemaker cells
  - increased fibrosis of cardiac fibrous skeleton
- **Renal function**[2]
  - decreased renal blood flow
  - decreased glomerular filtration rate
  - decreased creatinine clearance
- **Hepatic function**[3]
  - reduced hepatic blood flow
  - decline in cytochrome P450 system

1Cheitlin MD. Am J Geriatr Cardiol 2003;12:9-13
2Muhlberg W, et al. Gerontology 1999;45:243-53
3Anantharaju A, et al. Gerontology 2002;48:343-53

Elderly

Researchers have largely shied away from the complexity of multiple chronic conditions — avoidance that results in expensive, potentially harmful care of unclear benefit.

NEJM FREE FULL TEXT Tinetti M. NEJM2011

Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

Elderly patients…

Lung cancer and elderly.

- Elderly patients generally excluded from clinical trials
- Few specifically designed clinical trials
- Many believe that "biological" age rather than "chronological" age should guide medical decision
- No agreement on the definition of "elderly"

(65 – 70 – 75 years ?)

Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

IASLC

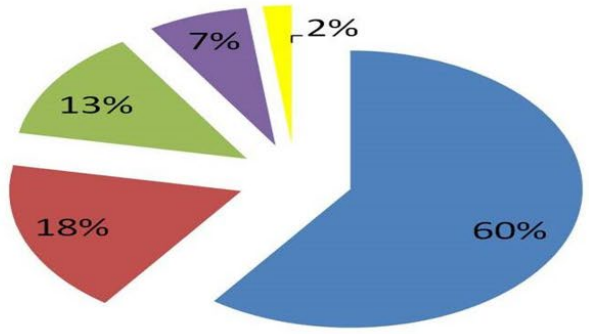
2019 World Conference on Lung Cancer

September 7–10, 2019 | Barcelona, Spain

Older Adults Remain Under-represented

Lung Cancer Patients Enrolled on Registration Trials Supporting FDA Approval

FDA



Lung Cancer trials:

- Non-small cell lung CA
- Squamous
- PD-1/PD-L1 specific
- ALK positive

42 trials N = 27032

What is the definition of elderly? What is the age cut-off?

Median Age at Diagnosis:

70

Most frequently diagnosed among people aged 65-74 (32.9%)

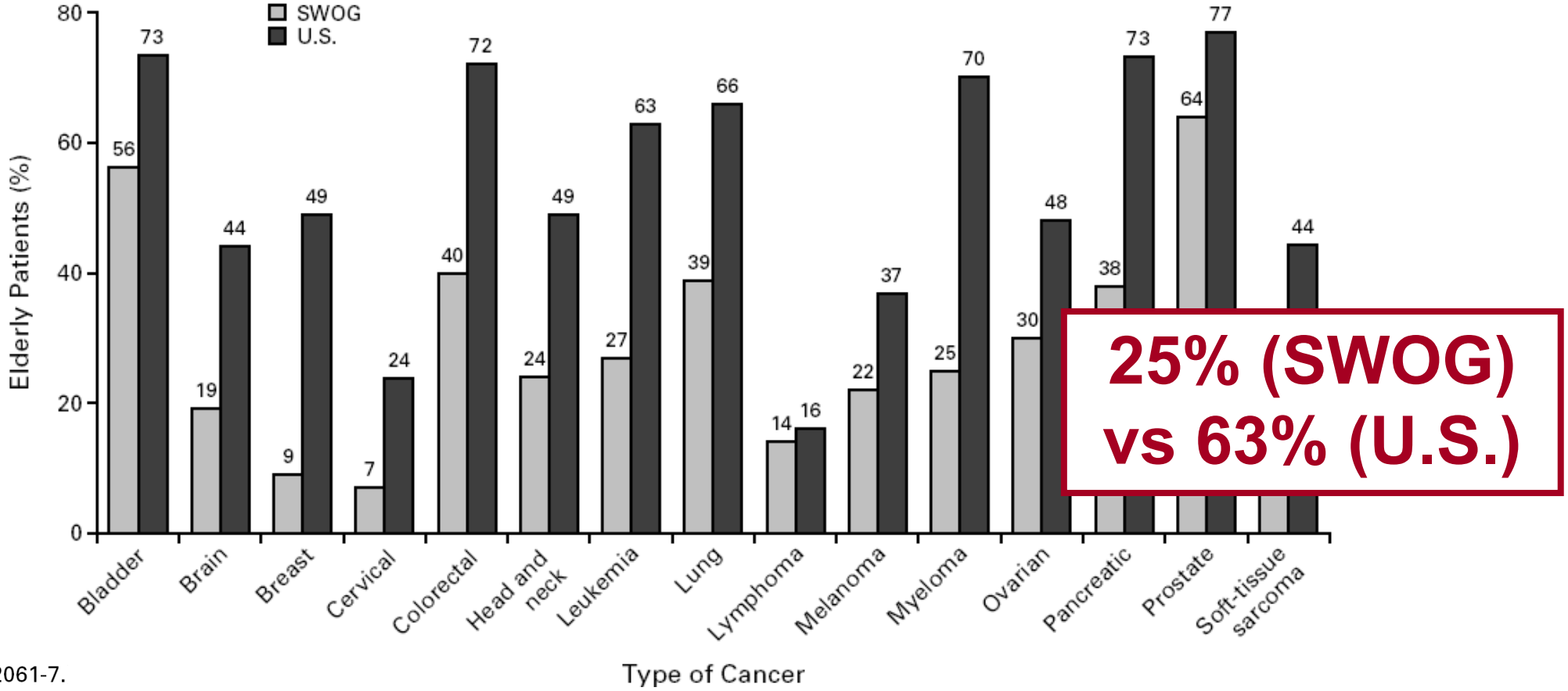
14

Presented by H. Singh, ASCO 2017

Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

UNDERREPRESENTATION OF PATIENTS 65 YEARS OF AGE OR OLDER IN CANCER-TREATMENT TRIALS

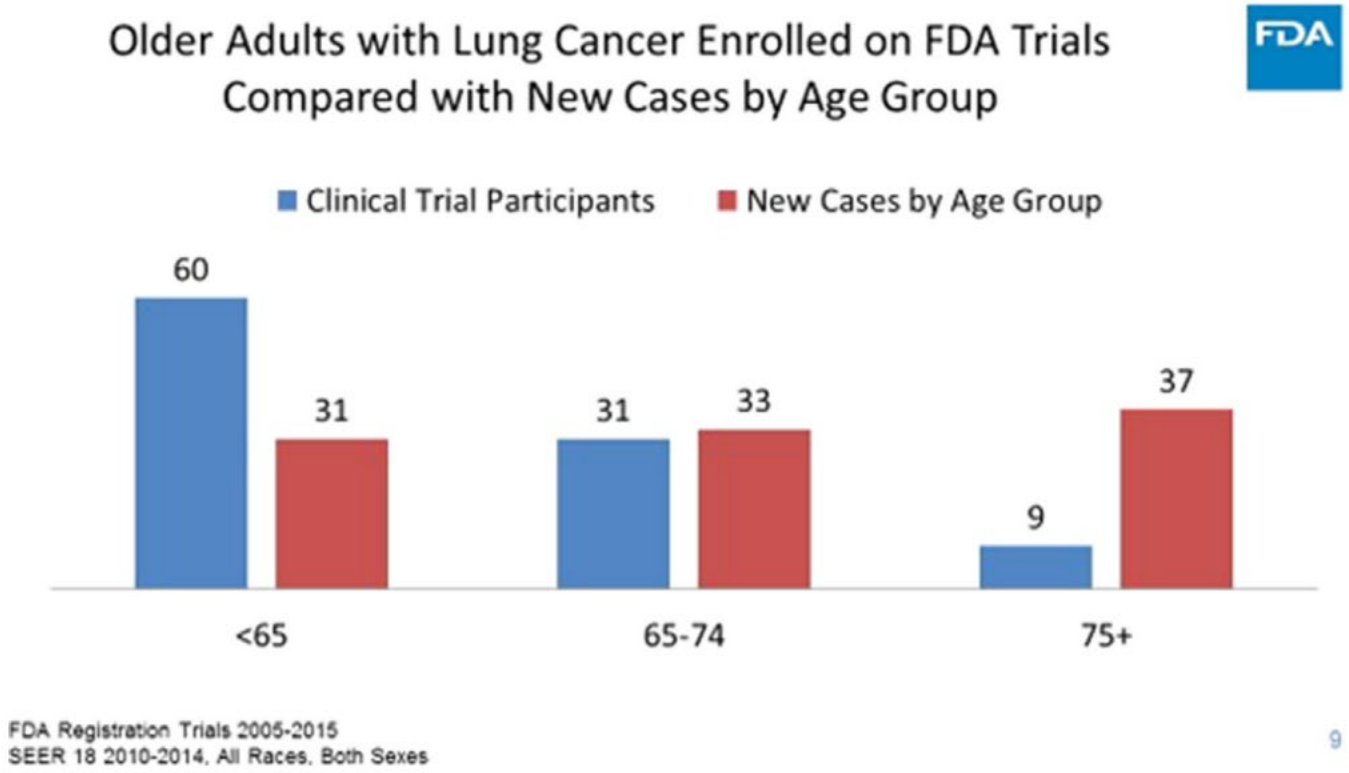
LAURA F. HUTCHINS, M.D., JOSEPH M. UNGER, M.S., JOHN J. CROWLEY, PH.D., CHARLES A. COLTMAN, JR., M.D., AND KATHY S. ALBAIN, M.D.



25% (SWOG) vs 63% (U.S.)

N Engl J Med 1999;341:2061-7.

Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial



S. Marur et al. / Seminars in Oncology 000 (2018) 1–6

RCT: potential and limits

- Gold standard of scientific evidence
- Irreplaceable in the evaluation of the effectiveness of new drugs (efficacy)
- The results may not be generalizable to all subjects who will use the drug in clinical practice (effectiveness)

Dieppe P, et al. BMJ 2004;329:31 2004;329:31-

Barriers to the recruitment of older patients with cancer onto clinical trials: a systematic review

Systematic review based on

- Population based studies
- Physician surveys
- Retrospective studies

J Clin Oncol 23:3112-3124.

Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

Table 1. Evidence Detailing the Nine Studies Used in the Systematic Review, by Year

Study	Year Published	Country	Description	Method	Phase	Age Cut-Off Used to Define Elderly (years)
Talarico et al[45]	2004	USA	Retrospective analysis of the accrual of elderly patients in trials for registration of new cancer drugs or new indications of marketed drugs approved by the FDA from 1995 to 2002, and compared with cancer demographic data from US Census and NCISEER	Retrospective review of trial data	II and III	65
Murthy et al[44]	2004	USA	Retrospective analysis of elderly patients enrolled onto NCICCG trials between 2000 and 2002, and compared with cancer demographic data from NCISEER	Retrospective review of trial data	II and III	65
Kemeny et al[47]	2003	USA	Interviews of 77 pairs of older and younger women matched by breast cancer stage and treating physician to determine reasons for participation *v* non-participation in an open cancer treatment trial for which all women were eligible; questionnaires were sent to treating physicians about reasons for offering or not offering trials to these patients	Retrospective case-control study	Not mentioned	65
Lewis et al[39]	2003	USA	Retrospective analysis of elderly patients enrolled onto NCI trials between 1997 and 2000, and compared with cancer demographic data from NCISEER	Retrospective review of trial data	II and III	65
Yee et al[40]	2003	Canada	Retrospective analysis of elderly patients enrolled onto NCIC CTG trials between 1993 and 1996, and compared with cancer demographic data from Statistics Canada and published rates by SWOG; a separate survey of selected Canadian physicians at a conference	Retrospective review of trial data physician survey	I, II, or III	65
Kornblith et al[46]	2002	USA	Mail survey of selected physicians treating breast cancer at 10 CALGB institutions regarding barriers to recruitment of elderly breast cancer patients	Physician survey	Not mentioned	65
Sateren et al[41]	2002	USA	Retrospective analysis of all patients enrolled onto NCI trials between 1998 and 1999, and compared with cancer demographic data from US Census and NCISEER	Retrospective review of trial data	I, II, or III	Divided as 60-69, 70-79, and 80+
Hutchins et al[42]	1999	USA	Retrospective analysis of elderly patients enrolled onto SWOG trials between 1993 and 1996, and compared with cancer demographic data from US Census and NCISEER	Retrospective review of trial data	Not mentioned	65
Trimble et al[43]	1994	USA	Retrospective analysis of elderly patients enrolled onto NCICCG trials in 1992, and compared with cancer demographic data from 1990 NCISEER	Retrospective review of trial data	II and III	65

A systematic review

Table 2. Comparison of Two Studies Using Physicians' and Patients' Information From Breast Cancer Clinical Trials From CALGB Institutions

Study	Objective and Methods	Important Findings	Discussion Points
Barriers to clinical trial participation by older women with breast cancer; Kemeny et al,[47] 2003	Retrospective case-control study to examine whether older breast cancer patients, seen at a CALGB institution, were offered trials less often, and whether they were more likely to refuse participation; 77 matched patients interviewed; physicians given questionnaires	Younger patients were offered entry onto a trial more often (68%) than older patients (34%; $P = .0004$). Interestingly, of those patients offered a trial, there was no significant difference in participation rates between older and younger patients	It appeared that the greatest barrier to the accrual of older patients was physician perceptions about age and tolerability of treatment. For both younger and older patients, the main reason to decline trial participation was their desire to choose their own treatments
Survey of oncologists' perceptions of barriers to accrual of older patients with breast carcinoma to clinical trials; Kornblith et al,[46] 2002	Prospective physician survey of 156 physicians who had treated breast cancer patients at CALGB institutions	Surveyed physicians felt that the most important barriers to older patient accrual were significant comorbid conditions, poor compliance for the elderly patient, treatment toxicity, and difficulty meeting the eligibility requirements	It seemed that physicians perceived the barriers to be multidimensional with factors such as protocol requirements, treatment-specific issues, social support, logistic issues, and the medical and cognitive condition of older patients all playing a potential role

J Clin Oncol 23:3112-3124.

Barriers to the recruitment of older patients with cancer onto clinical trials

Barriers related to cancer trial design

- Hematologic, hepatic, renal or cardiac abnormalities
- Performance Status
- Previous cancer

J Clin Oncol 23:3112-3124.

Barriers to the recruitment of older patients with cancer onto clinical trials: a systematic review

Barriers related to physician factors

- Comorbid condition
- Toxicity of treatment
- Lack of support at home
- Low cultural level, fear
- Dependence on family members, caregivers, MM
- Life expectancy
- Geographic inaccessibility

Case Control Study CALGB institution

- Increasing age
- Late stage disease
- Comorbidities

J Clin Oncol 21: 2268-2275, 2003

Barriers to the recruitment of older patients with cancer onto clinical trials

Barriers Related to Patient Factors

When younger patients were asked their reasons for participating in a trial, the three most common reasons were: an improvement in their health, to find a cure for cancer, and a desire for the most updated treatment. For older patients, the most common reasons for participating were: it was the best treatment available, an improvement in their health, and to find a cure for cancer.
The primary reason for not participating in a study for younger patients was that they wanted to choose their own treatment. The older patients also chose this reason most frequently for their refusal to take part in a study

J Clin Oncol 21: 2268-2275, 2003

Is the elderly patient a possible patient to be enrolled in a clinical trial?

Protocol Design Barriers

Inadequate" performance status may be difficult to interpret

Previous malignancy (the inclusion of patients with a reasonable time frame since their previous cancer)

The functional assessment of the geriatric patient

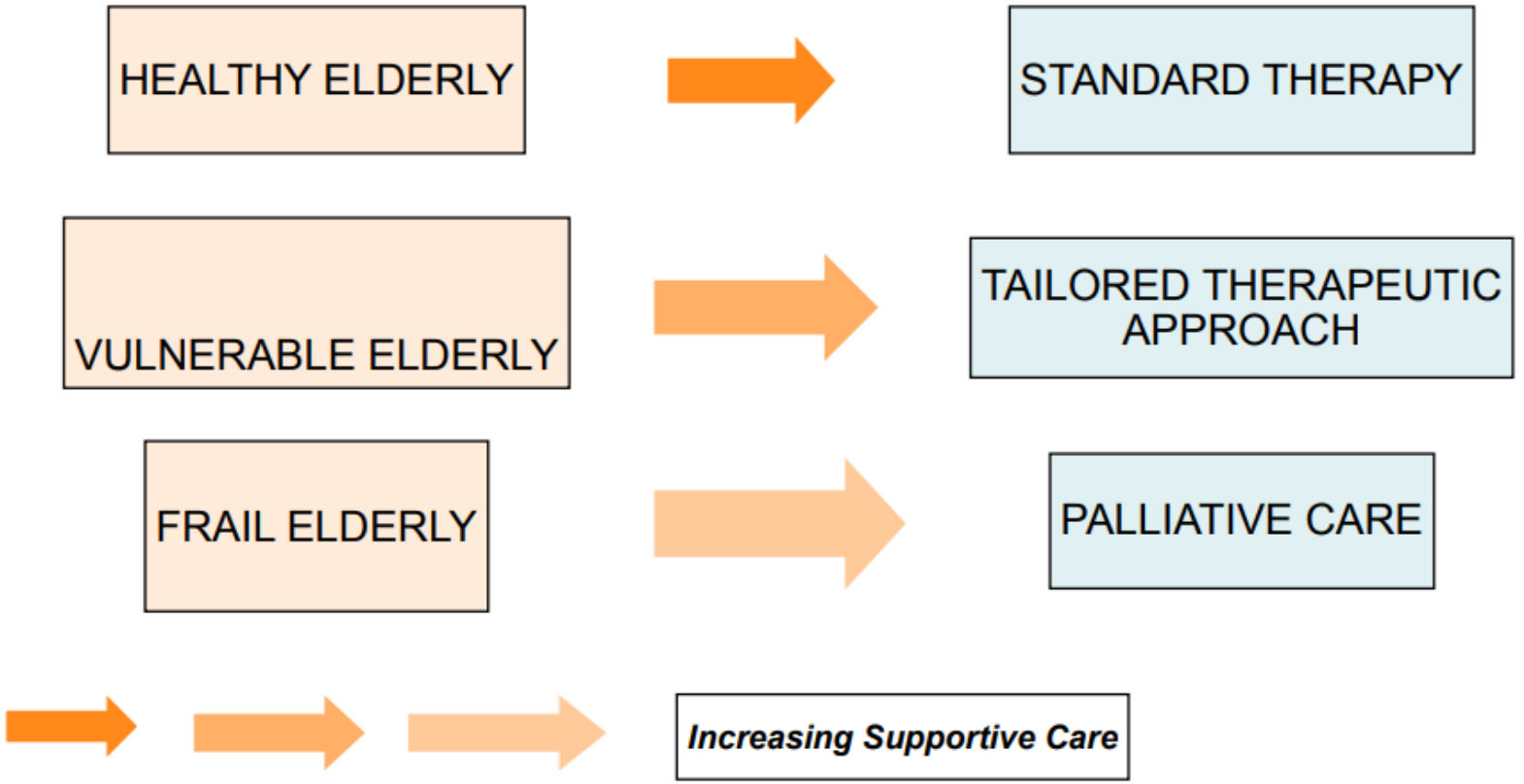
J Clin Oncol 21: 2268-2275, 2003

COMPREHENSIVE GERIATRIC ASSESSMENT CGA

- **Function**
  - PS
  - ADL
  - IADL
  - AADL
- **Comordidity**
  - Charlson scale
- **QoL**
  - Disease-specific questionnaries

- **Cognition**
  - MMS
- **Emotion**
  - GDS
- **Social support**
- **Polypharmacy**
- **Nutrition**

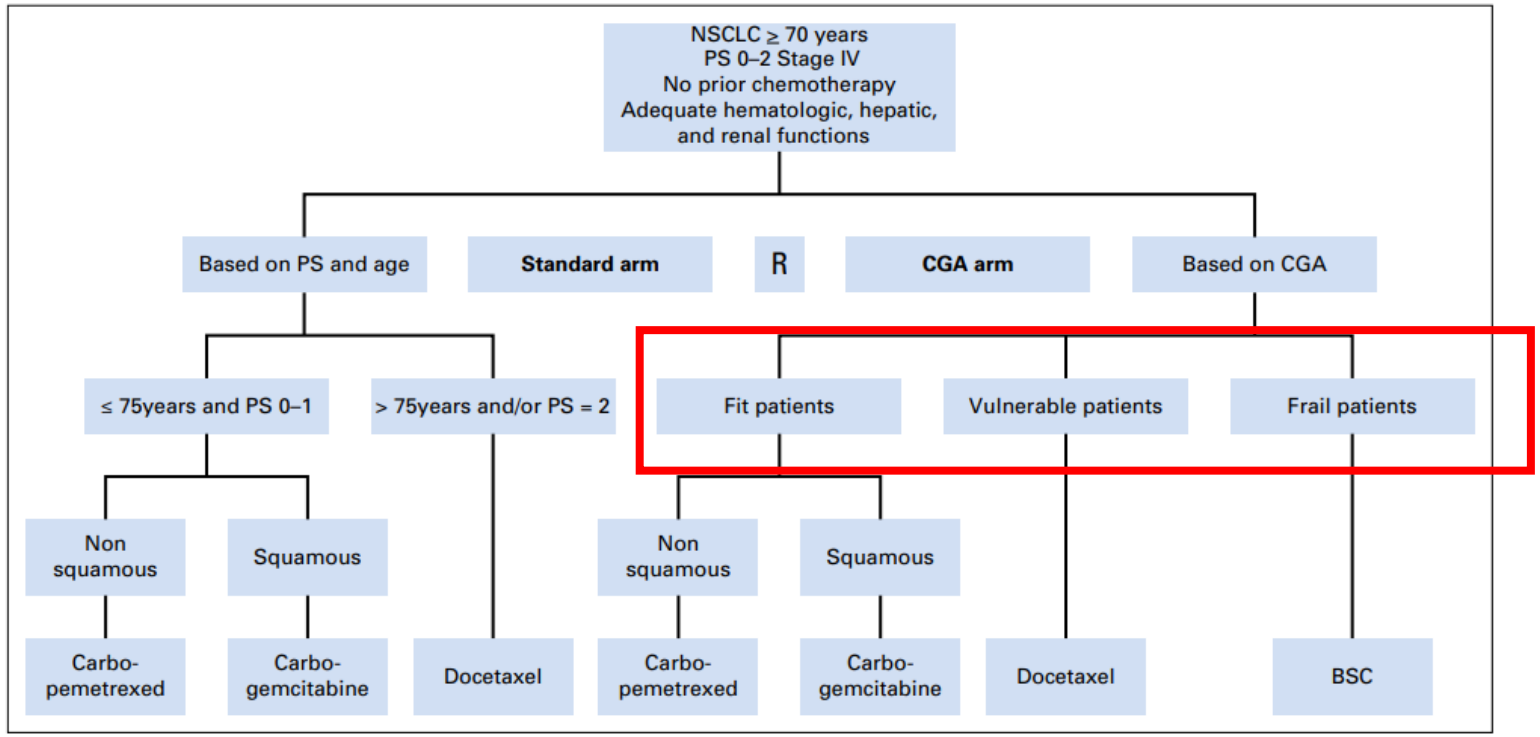
COMPREHENSIVE GERIATRIC ASSESSMENT CGA



Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study



J Clin Oncol 34:1476-1483. © 2016

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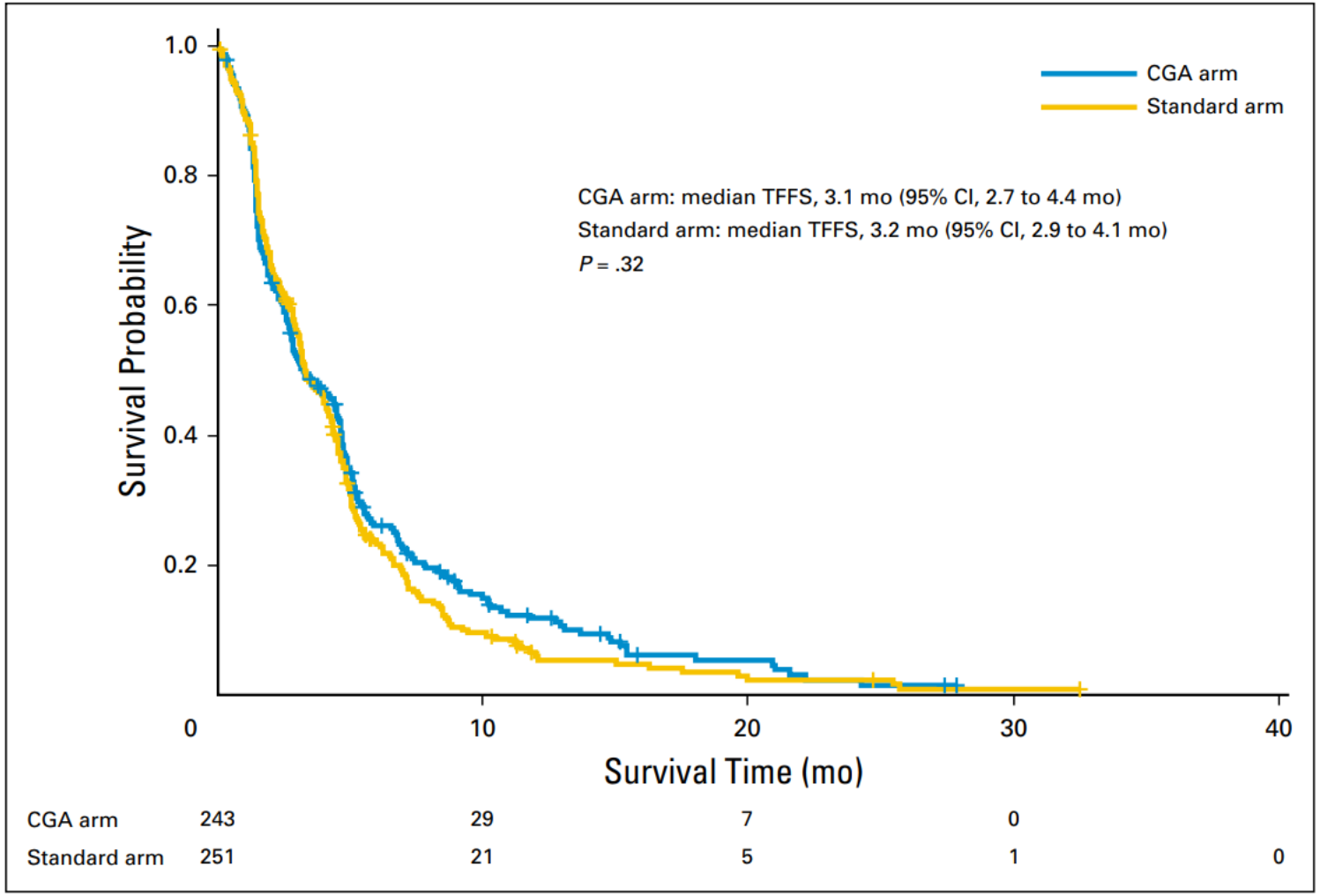
Table 1. Definition of Fit, Vulnerable, and Frail Patients in the CGA Arm

Geriatric Parameters	Fit: All Criteria	Vulnerable: One of the Bold Criteria	Frail: One of the Bold Criteria
PS	0 or 1	**2**	0-2
ADL (0-6)	6	6	**≤ 5**
IADL (0-4)	0	**1**	**≥ 2**
Schultz-Larsen MMSE (0-11)	≥ 9		
Folstein MMSE (0-30)		> 23	**≤ 23**
Geriatric syndrome	No	No	**Yes**
Charlson comorbidity index	0-1	**2-3**	**≥4 (≥ 3 if > 80 years)**
GDS5 (0-5)	0-1	**2-3**	**4-5**

J Clin Oncol 34:1476-1483. © 2016

The Phase III Randomized ESOGIAGFPC-GECP 08-02 Study

Treatment failure–free survival (TFFS) over the duration of the study: no difference



J Clin Oncol 34:1476-1483. © 2016

The Phase III Randomized ESOGIAGFPC-GECP 08-02 Study

Toxicity: slight improvement

Table 4. Grade 3 or 4 Toxicities

Toxicity	% of Patients		
	Standard Arm (n = 251)	CGA Arm (n = 242)	P
All grades	93.4	85.6	.01
Grade 3-4	71.3	67.9	.41
Grade 3-4 neutropenia			.41
All	11.1	13.2	
Doublet	16.0	25.2	
Monotherapy	8.0	5.3	
BSC	—	0	
Grade 3-4 febrile neutropenia			.22
All	5.6	3.3	
Doublet	11.0	5.4	
Monotherapy	2.4	2.6	
BSC	—	0	
Grade 3-4 anemia			.87
All	11.2	10.7	
Doublet	21.6	16.2	
Monotherapy	5.5	6.6	
BSC	—	5.3	
Grade 3-4 thrombocytopenia			.04
All	3.6	7.8	
Doublet	7.9	17.1	
Monotherapy	1.2	0	
BSC	—	0	
Grades 3-4 asthenia			.34
All	10.8	13.6	
Doublet	7.9	14.4	
Monotherapy	12.3	15.8	
BSC	—	8.9	
Grade 3-4 anorexia			.27
All	4.0	6.2	
Doublet	0	10	
Monotherapy	6.0	5.3	
BSC	—	0	
Grade 3-4 nausea/vomiting			.46
All	3.6	4.9	
Doublet	1.1	8.1	
Monotherapy	4.9	2.6	
BSC	—	1.8	
Grade 3-4 peripheral sensory neuropathy			.62
All	1.2	0.4	
Doublet	0	0	
Monotherapy	1.8	1.3	
BSC	—	0	

J Clin Oncol 34:1476-1483. © 2016

Patient Barriers

The patients' desire to choose their own treatment
Additional time to explain the purpose of clinical trials (risks and benefits, the details of a specific clinical trial and the consent form): **patient's education**

Support systems (transportation, management of treatment-related adverse effects, and maintenance of any central or peripheral intravenous lines required for the study)

J Clin Oncol 21: 2268-2275, 2003

Physician Barriers

Paucity of primary research related to biology of cancer, toxicity and effect of treatment on comorbidities

Breast cancer and lung cancer: similar toxicity and efficacy

J Clin Oncol 21: 2268-2275, 2003

Elderly patient and clinical trials: evidence from NSCLC

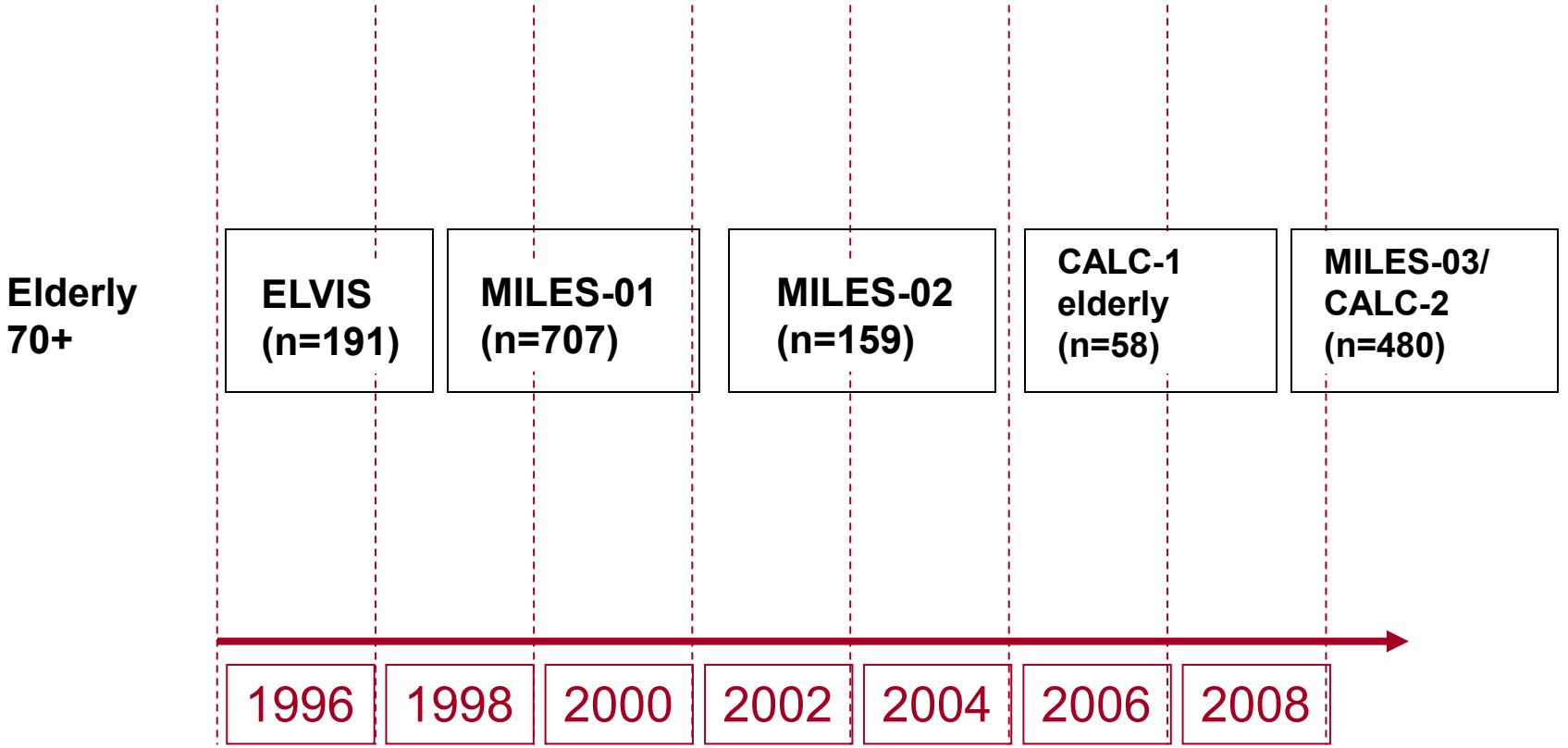
Elderly population and lung cancer

- Monochemotherapy (Elvis-Miles)
- MILES trials: doublet with Platinum in selected patients (Miles 3-4), CT and ICI (Miles 5)
- Adjuvant trial

- PD-L1: > 50%
- Single agent immunotherapy (KN024 – KN042)
- monoCT in pts unfit for IO

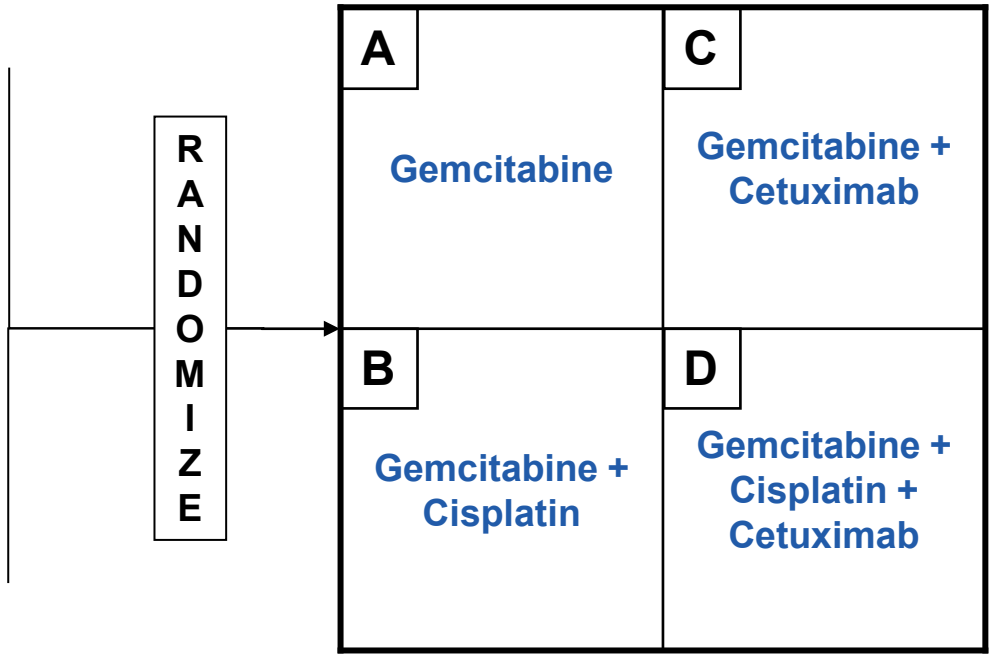
- PD-L1: 1- 49%
- Monochemotherapy or platinum doublet
- "Fit" immuno-combo (KN189 - KN407)
- In subsequent lines IO (OAK – KN010 – CM017 – CM057)

Trials in elderly NSCLC patients



Trials in elderly NSCLC patients: MILES-03/CALC-02

Patient population
- **NSCLC**
- **Age =>70**
- **PS 0-1**
- **Stage IIIb-IV**



Two comparisons planned:

A+B vs C+D testing efficacy of cetuxomab

A+C vs B+D testing efficacy of cisplatin

361 events required to demonstrate **superiority** in survival

480 patients planned

A: Gemcitabine, 1200 mg/m^2, day 1 and 8 every 3 weeks, for 6 cycles
B: Gemcitabine, 1000 mg/m^2, day 1 and 8 + Cisplatin, 60 mg/m^2, day 1 every 3 weeks, for 6 cycles
C: as A + Cetuximab, 400 mg/m^2 (1st dose) then 250 mg/m^2 weekly until progression
D: as B + Cetuximab, 400 mg/m^2 (1st dose) then 250 mg/m^2 weekly until progression

Trials in elderly NSCLC patients: adjuvant trial

VOLUME 25 · NUMBER 12 · APRIL 20 2007

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Adjuvant Vinorelbine and Cisplatin in Elderly Patients: National Cancer Institute of Canada and Intergroup Study JBR.10

Carmela Pepe, Baktiar Hasan, Timothy L. Winton, Lesley Seymour, Barbara Graham, Robert B. Livingston, David H. Johnson, James R. Rigas, Keyue Ding, and Frances A. Shepherd

Agent	Dose	Schedule	
Cisplatin	50 mg/m^2	D 1 & 8	Q 4 weeks x 4 cycles
Vinorelbine	30 mg/m^{2*}	1+8+15+22	Q 4 wks X 4 cycles
	25 mg/m^2	1+8+15+22	X 4 cycles

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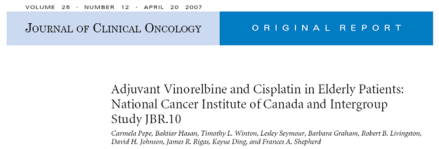
Dose Intensity

Drug	Young (age ≤65) N= 150		Elderly (age >65) N= 63		p-value
	N Patients	%	N Patients	%	
Vinorelbine					
< 10 doses	76	50.7	45	71.4	0.014
10-14 doses	70	46.7	18	28.6	
16 doses	4	2.7	0	0	
Dose intensity (mg/m^2/week)	13.2		10.0		0.0004

Drug	Young (age ≤65) N= 150		Elderly (age >65) N= 63		p-value
	N Patients	%	N Patients	%	
Cisplatin					
< 5 doses	41	27.3	31	49.2	0.006
5-7 doses	32	21.3	12	19.1	
8 doses	77	51.3	20	31.8	
Dose intensity (mg/m^2/week)	18.0		14.1		0.001

Trials in elderly NSCLC patients: adjuvant trial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Carmela Pope, Bakhtiar Hasan, Timothy L. Winton, Lesley Seymour, Barbara Graham, Robert B. Livingston, David H. Johnson, James R. Rigas, Keyue Ding, and Frances A. Shepherd

Chemotherapy Toxicity

- No differences in G-CSF use
- No differences in hospitalizations
- 1 treatment-related death in both groups

Hematologic Toxicity	Young (age ≤65) N= 150		Elderly (age >65) N= 63		p-value
	N (%) Total	N (%) Grade 3 or 4	N (%) Total	N (%) Grade 3 or 4	
Anemia	127 (84.7)	10 (6.7)	53 (84.1)	6 (9.5)	0.47
Platelets	43 (28.7)	2 (1.3)	21 (33.3)	1 (1.6)	0.89
Neutropenia	122 (81.3)	100 (66.7)	49 (77.8)	41 (65.1)	0.82
Febrile Neutropenia		8 (5.3)		5 (7.9)	0.53

Non-Hematologic Toxicity	Young (age ≤65) N= 150		Elderly (age >65) N= 63		p-value
	N (%) Total	N (%) Grade 3 or 4	N (%) Total	N (%) Grade 3 or 4	
Nausea	125 (83.3)	14 (9.3)	44 (69.8)	8 (12.7)	0.46
Vomiting	73 (48.7)	10 (6.7)	29 (46.0)	5 (7.9)	0.74
Anorexia	87 (58.0)	12 (8.0)	28 (44.4)	8 (12.7)	0.28
Lethargy	125 (83.3)	19 (12.7)	47 (74.6)	9 (14.3)	0.75
Constipation	67 (44.7)	5 (3.3)	32 (50.8)	1 (1.6)	0.48
Neuropathy	77 (51.3)	4 (2.7)	23 (36.5)	1 (1.6)	0.63
Myalgias	21 (14.0)	0 (0)	4 (6.3)	1 (1.6)	0.12

Despite similar toxicities, elderly patients received significantly less chemotherapy

Fewer elderly completed all treatment
40% elderly vs 56% young
More elderly refused treatment
40% elderly vs 23% young

p=0.025

Trials in elderly NSCLC patients: adjuvant trial

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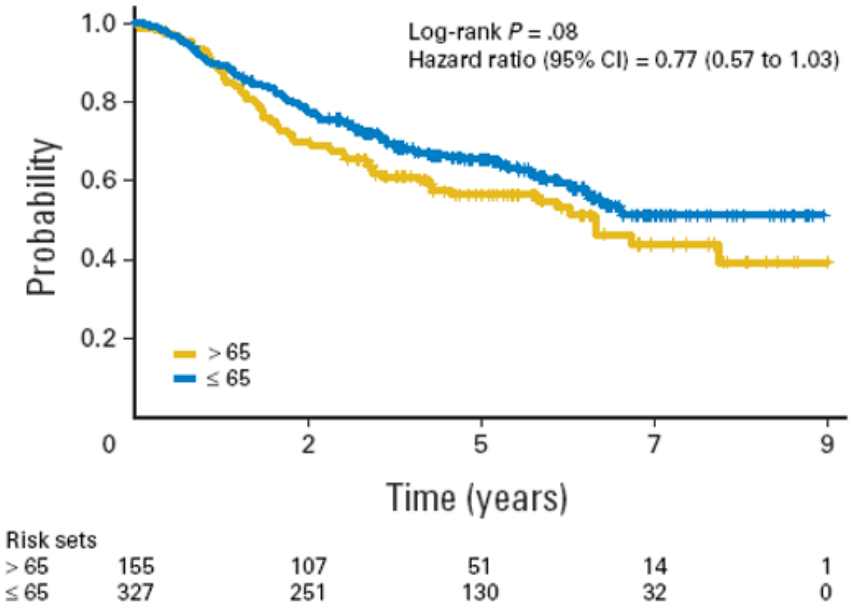
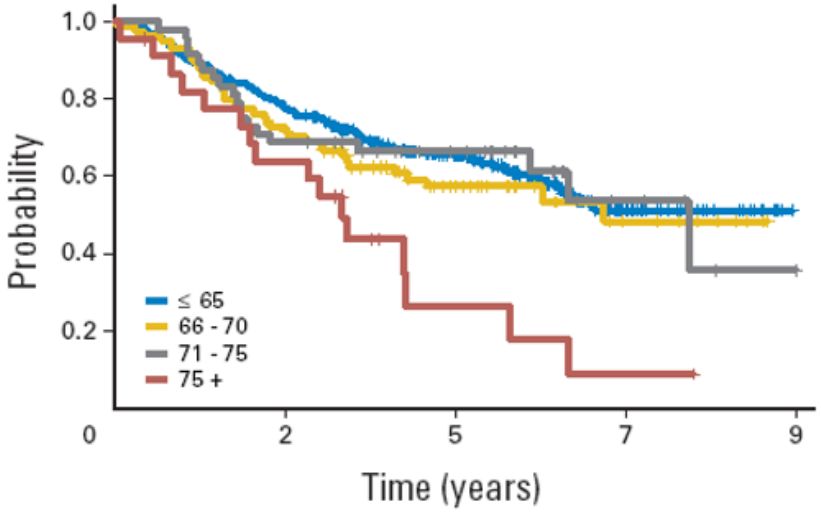
Carmela Pepe, Bakhtiar Hasan, Timothy L. Winton, Lesley Seymour, Barbara Graham, Robert B. Livingston, David H. Johnson, James R. Rigas, Keyue Ding, and Frances A. Shepherd

Overall Survival all randomized patients, by Age Group



Risk sets					
> 65	155	107	51	14	1
≤ 65	327	251	130	32	0



Risk sets					
≤ 65	327	251	130	32	0
66 - 70	84	60	27	8	0
71 - 75	48	33	21	5	1
75 +	23	14	3	1	0

Trials in elderly NSCLC patients: adjuvant trial

Adjuvant Vinorelbine and Cisplatin in Elderly Patients: National Cancer Institute of Canada and Intergroup Study JBR.10

Carmela Pepe, Baktiar Hasan, Timothy L. Winton, Lesley Seymour, Barbara Graham, Robert B. Livingston, David H. Johnson, James R. Rigas, Keyue Ding, and Frances A. Shepherd

Conclusions

- **Adjuvant platinum-based chemotherapy can be given safety to elderly patients, without significant risk of increased toxicity**
- **Despite receiving less chemotherapy compared to young patients, elderly patients derive a substantial survival benefit from adjuvant therapy**
- **Chemotherapy in the adjuvant setting should not be withheld from elderly patients on the basis of age alone**
- **Patients aged >75 require further study**

Pepe C et al J Clin Oncol 25:1553-1561, 2007

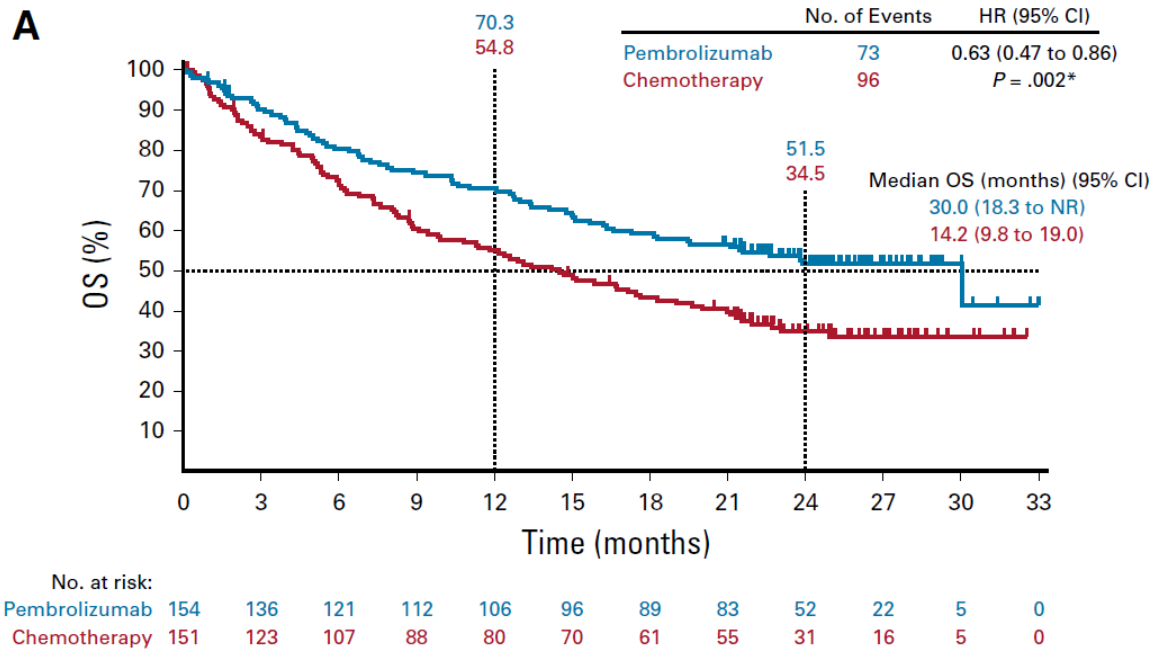
Elderly population and lung cancer

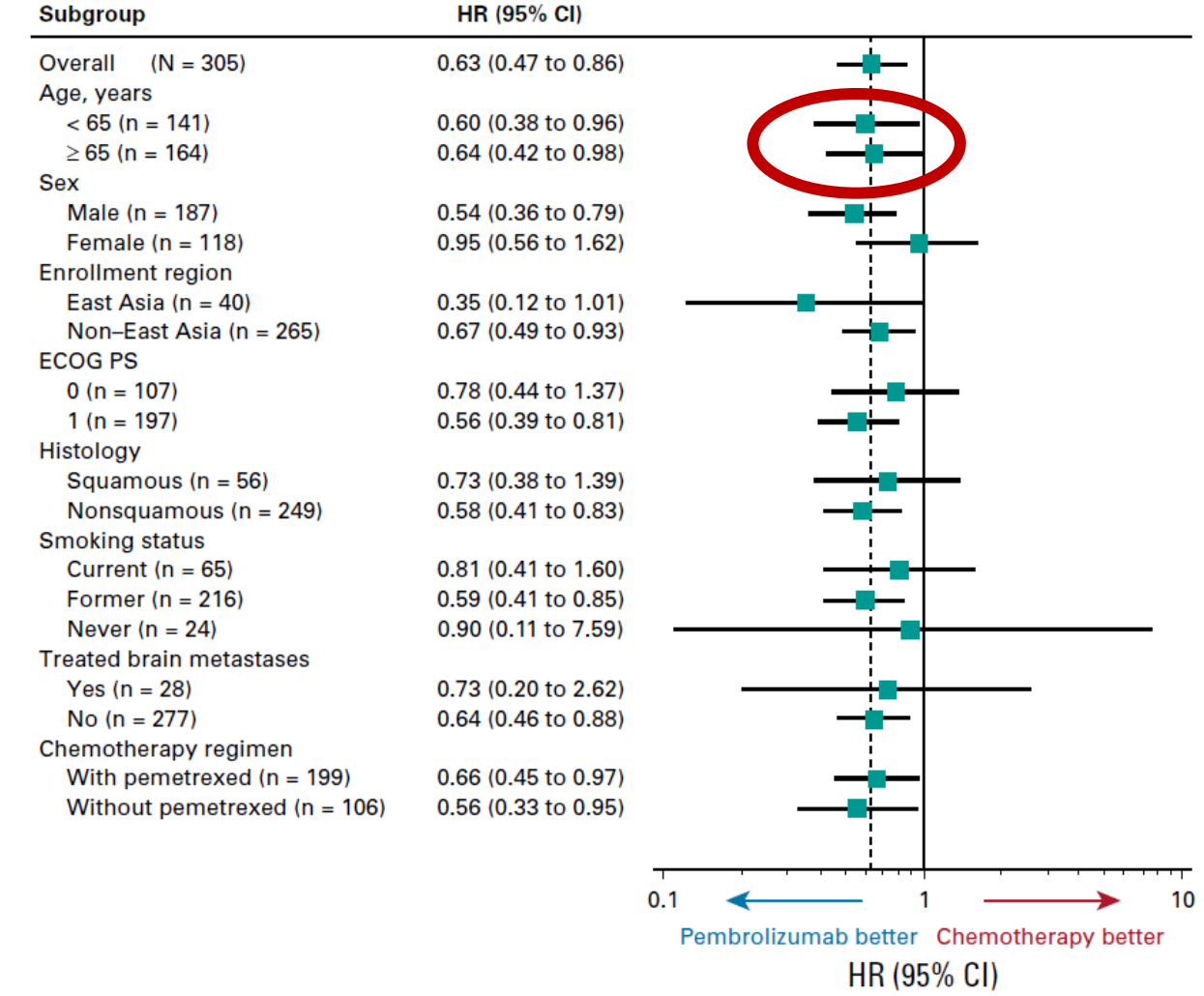
- Monochemotherapy (Elvis-Miles)
- Doublet with Platinum in selected patients (Miles 3-4)
- Adjuvant trial

- PD-L1: > 50%
- Single agent immunotherapy (KN024 – KN042)
- monoCT in pts unfit for IO

- PD-L1: 1- 49%
- Monochemotherapy or platinum doublet
- "Fit" immuno-combo (KN189 - KN407)
- In subsequent lines IO (OAK – KN010 – CM017 – CM057)

Keynote 024:elderly OS >65 aa- TPS≥50 %





Pool analysis KN 010, KN024,KN042 in elderly

K Nosaki. ELCC 2019.

Background

- Pembrolizumab, an anti–PD-1 immunotherapy, has proven efficacy in patients with advanced NSCLC with PD-L1–positive tumors
- Elderly patients (≥75 years of age) are underrepresented in clinical trials[4-6]
- We present a pooled analysis of elderly patients (≥75 years) from KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 to evaluate the efficacy and safety of pembrolizumab monotherapy

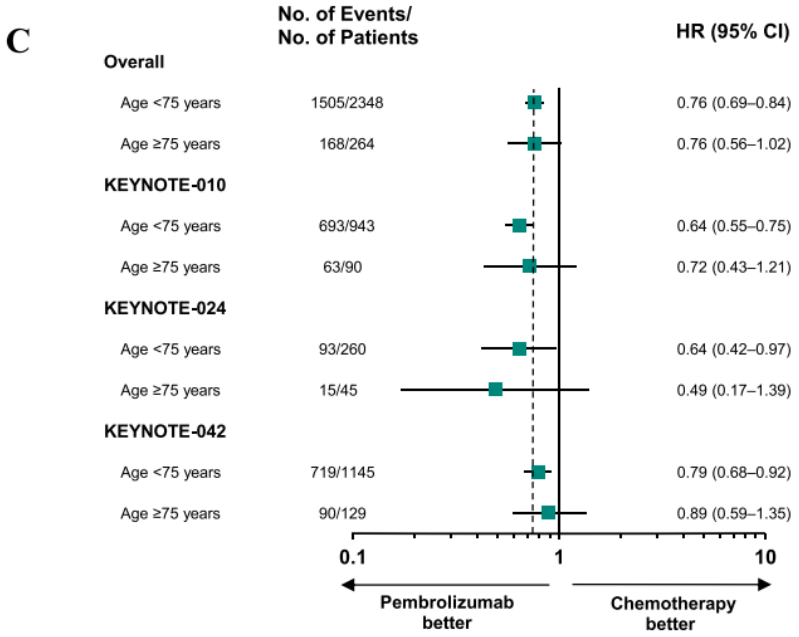
Clinical Study	Trial Design	OS HR (95% CI)
KEYNOTE-010[1] (KN010) phase 2/3	• Pembrolizumab (2 mg/kg or 10 mg/kg Q3W) vs docetaxel • Previously treated advanced NSCLC • PD-L1 TPS ≥1%	2 mg/kg, 0.71 (0.58–0.88), *P* = 0.0008 10 mg/kg, 0.61 (0.49–0.75), *P*<0.0001
KEYNOTE-024[2] (KN024) phase 3	• Pembrolizumab 200 mg Q3W vs platinum-based chemotherapy • Previously untreated advanced NSCLC • PD-L1 TPS ≥50%	0.60 (0.41–0.89), *P* = 0.005
KEYNOTE-042[3] (KN042) phase 3	• Pembrolizumab 200 mg Q3W vs platinum-based chemotherapy • Previously untreated advanced NSCLC • PD-L1 TPS ≥1%	PD-L1 TPS ≥1%, 0.81 (0.71–0.93), *P* = 0.0018 PD-L1 TPS ≥50%, 0.69 (0.56-0.85), *P* = 0.0003

1. Herbst, et al. *Lancet*. 2016;387:1540-50; 2. Reck, et al. *NEJM*. 2016;375:1823-33; 3. Mok, et al. *Lancet*. 2019 Apr 4. [Epub]; 4. Noone, et al. SEER Cancer Statistics Review, 1975-2015. Bethesda, MD: National Cancer Institute, 2018; 5. Talarico, et al. *J Clin Oncol*. 2004;22:4626-31; 6. Singh, et al. *J Clin Oncol*. 2017;35:10009.

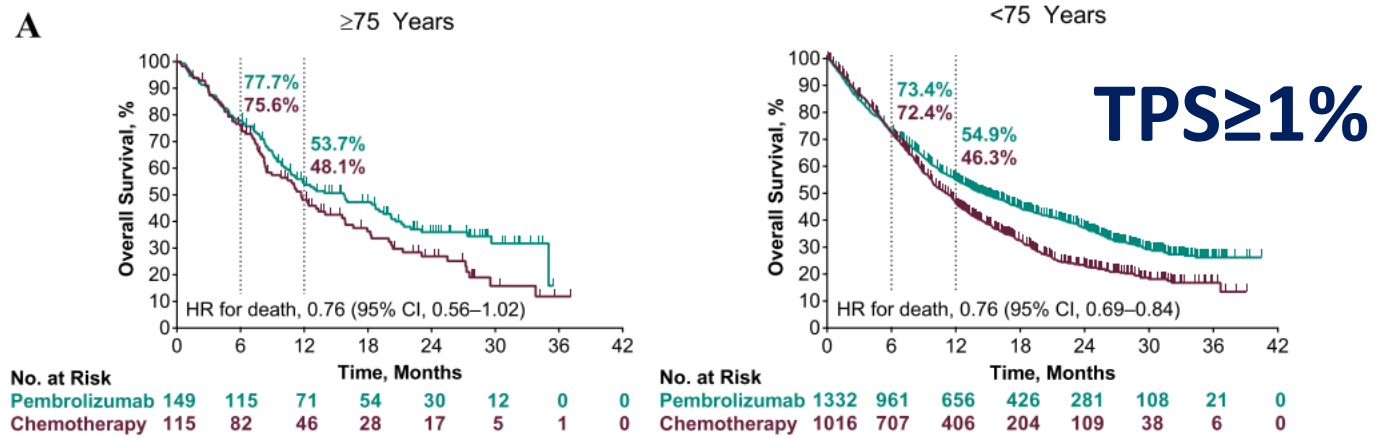
Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1–positive advanced non–small-cell lung cancer: Pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies

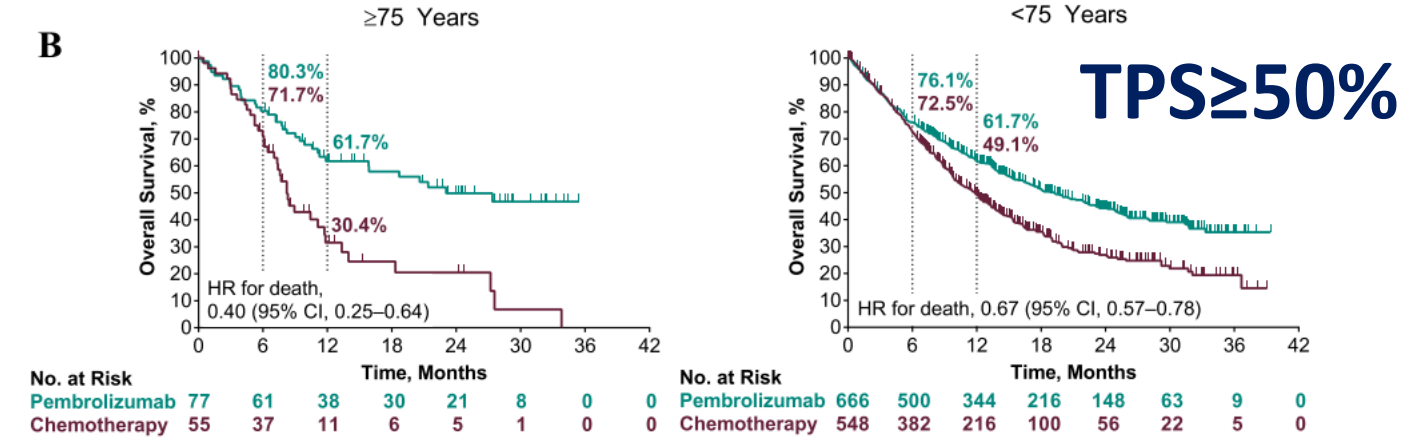
Kaname Nosaki[a,1,*], Hideo Saka[b], Yukio Hosomi[c], Paul Baas[d], Gilberto de Castro Jr.[e], Martin Reck[f], Yi-Long Wu[g], Julie R. Brahmer[h], Enriqueta Felip[i], Takeshi Sawada[j], Kazuo Noguchi[j], Shi Rong Han[j], Bilal Piperdi[k], Debra A. Kush[k], Gilberto Lopes[l]



Pembrolizumab improved OS compared with chemotherapy



TPS≥1%

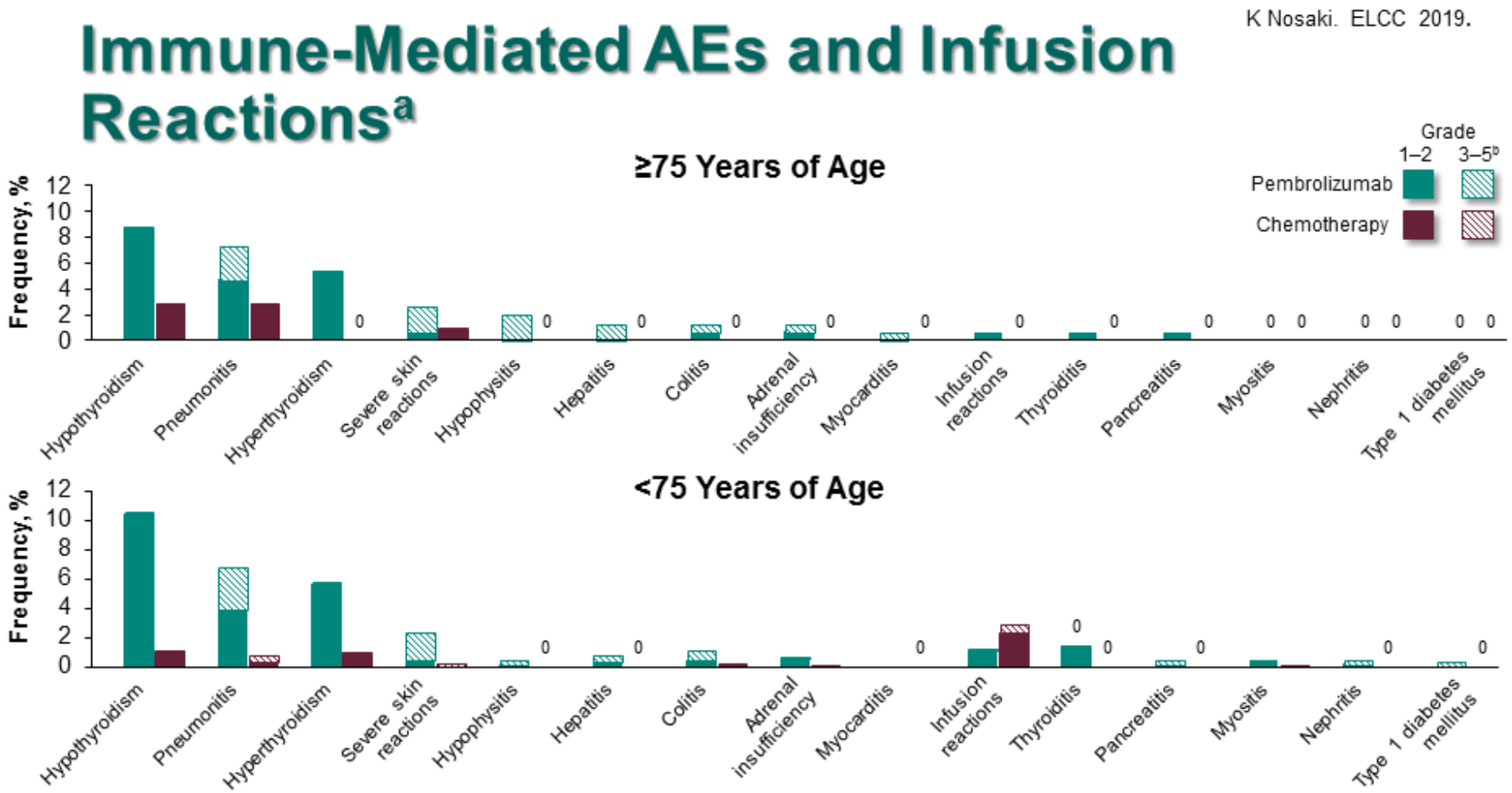


TPS≥50%

Lung Cancer 135 (2019) 188–195

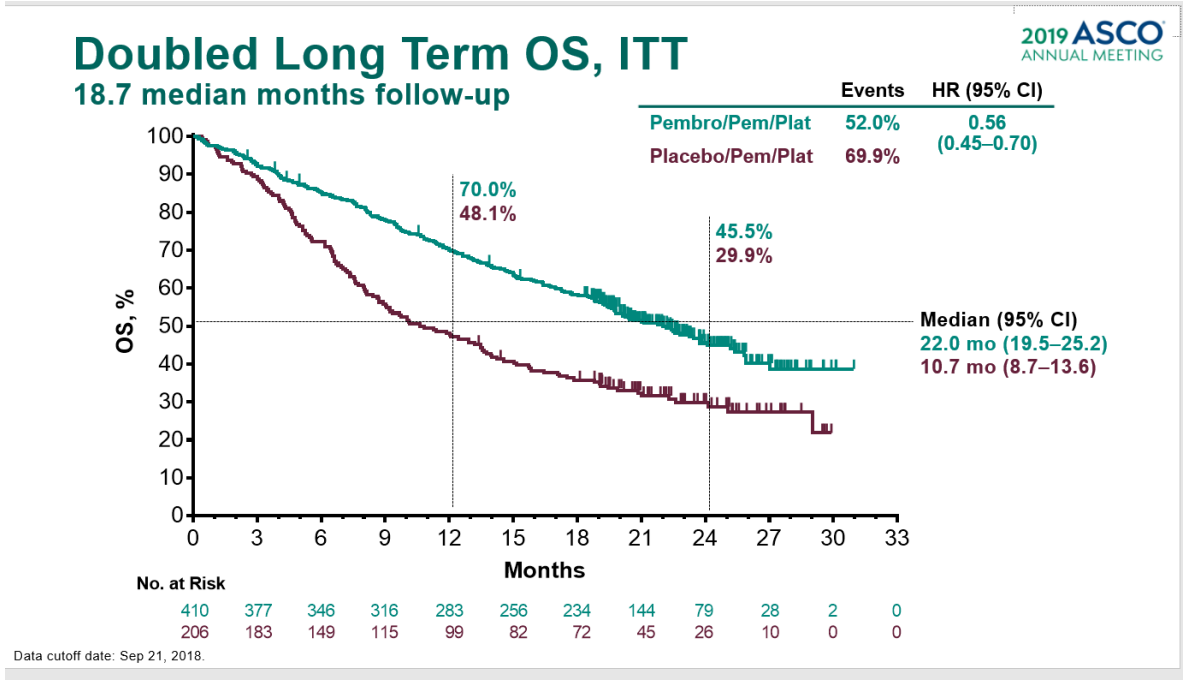
Pool analysis KN 010, KN024,KN042 in elderly

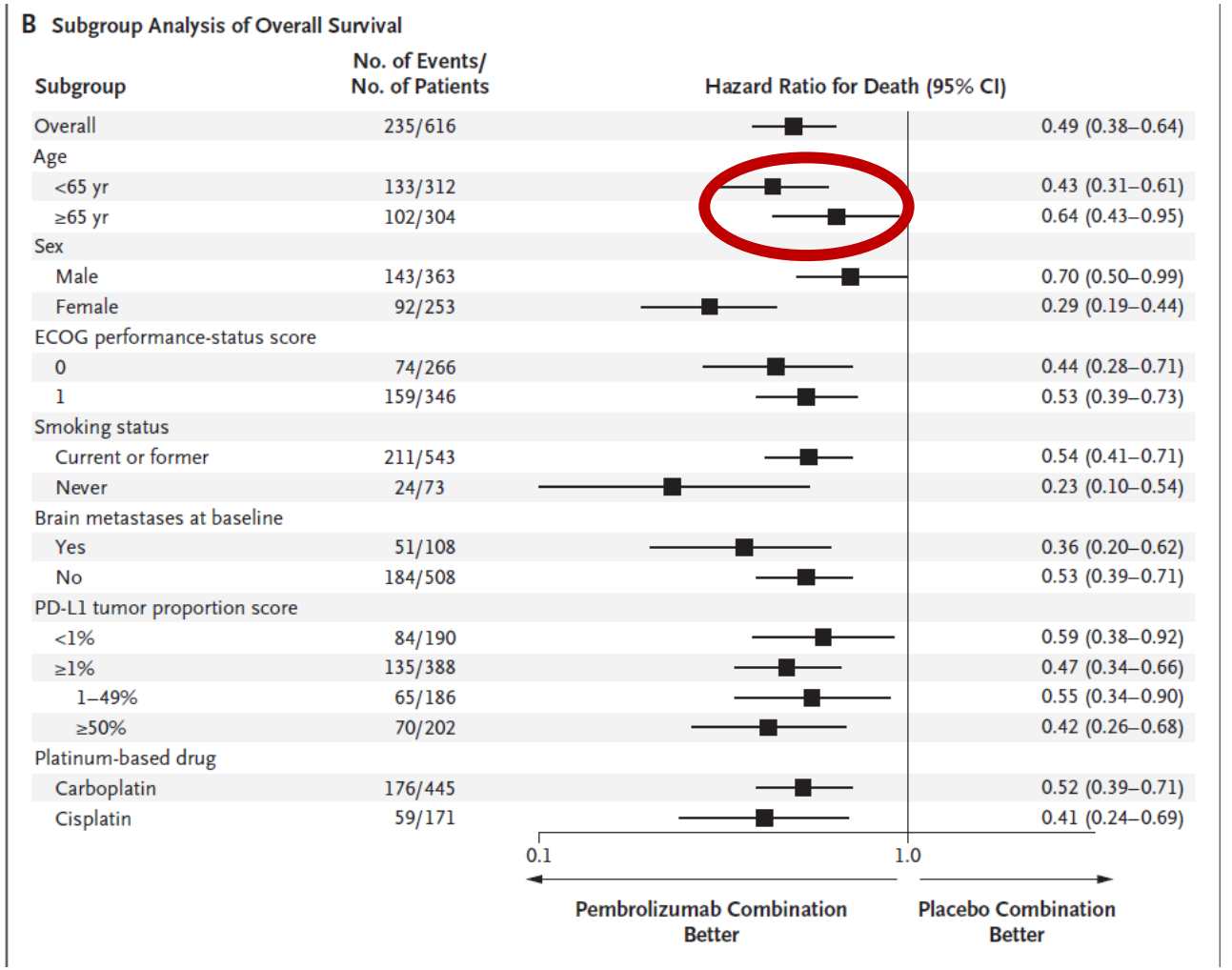
K Nosaki. ELCC 2019.



[a]Irrespective of attribution to treatment by the investigator. [b]There were no immune-mediated AEs or infusion reactions leading to death among patients ≥75 years of age.
Data cutoff dates: KN010, March 24, 2017; KN024, May 9, 2016; KN042, February 26, 2018.

Keynote 189: elderly OS >65 aa

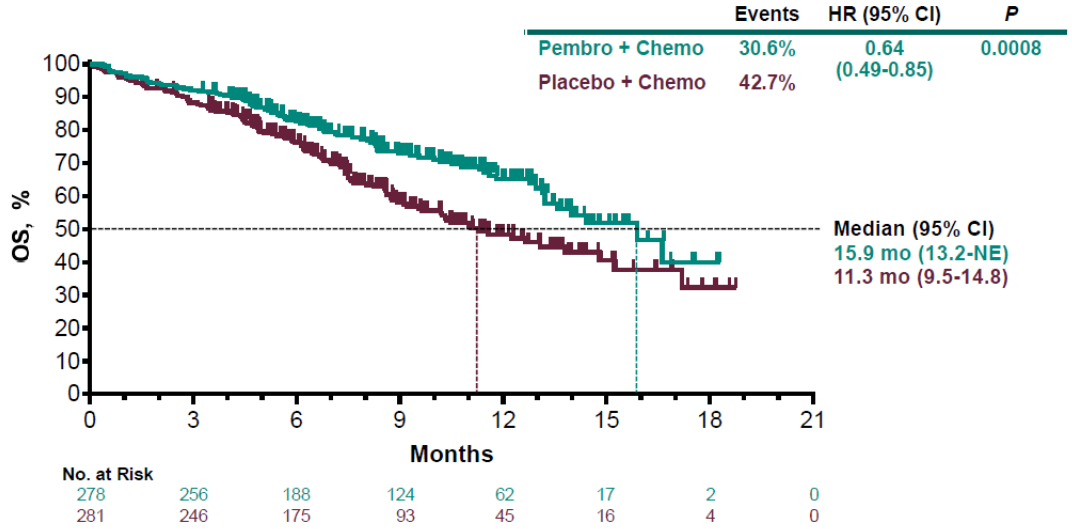




Keynote 407:elderly OS >65 aa

Paz-Ares KN407 ASCO 2018

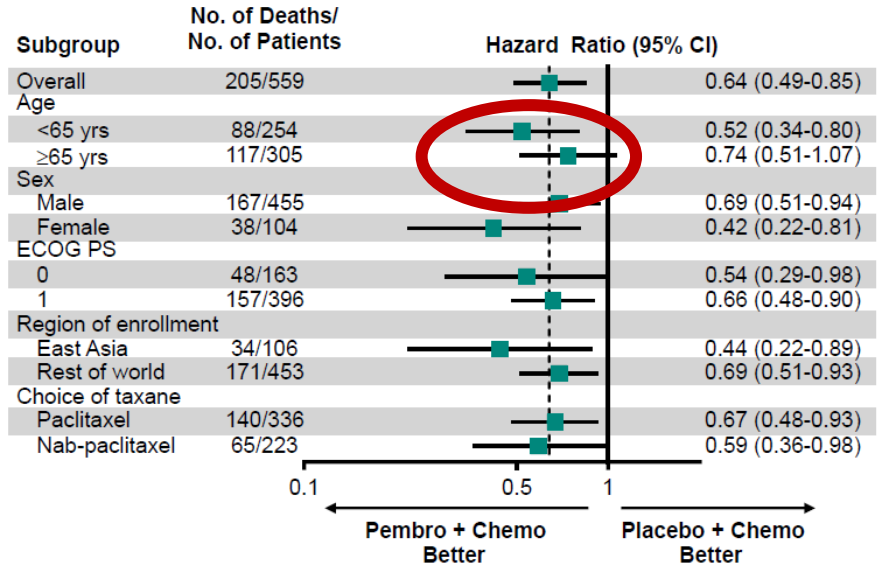
Overall Survival at IA2, ITT



Data cutoff date: Apr 3, 2018.

Paz-Ares KN407 ASCO 2018

Overall Survival at IA2 in Key Subgroups



Data cutoff date: Apr 3, 2018.

Second line NSCLC trials

Table 1
Second line NSCLC Trials comparing PD-1/PD-L1 blocking antibodies to chemotherapy.

Study (NCT number)	Treatment arm (anti-PD-1/PD-L1)	Control arm	Overall survival results (HR, 95% CI)
CheckMate 057 (NCT01673867)	Nivolumab 2 mg/kg IV q 2 wk	Docetaxel	0.73 (0.60,0.89)
KN-010 (NCT01905657)	Pembrolizumab 2 mg/kg IV q 3 wk	Docetaxel	0.71 (0.58, 0.88)
	Pembrolizumab 10 mg/kg IV q 3 wk	Docetaxel	0.61 (0.49, 0.75)
OAK (NCT02008227)	Atezoluzimab 1,200 mg IV q 3 wk	Docetaxel	0.73 (0.63, 0.87)
POPLAR (NCT01903993)	Atezoluzimab 1,200 mg IV q 3 wk	Docetaxel	0.73 (0.52, 0.92)

CI = confidence interval; HR = hazard ratio; NSCLC = non–small cell lung cancer; PD-1 = programmed death 1 receptor; PD-L1 = programmed death ligand 1.

S. Marur et al. / Seminars in Oncology 000 (2018) 1–6

Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

Table 2
Pooled baseline demographics by age group patients treated with PD-1/PD-L1 blocking antibodies for disease progression on or after platinum-based therapy ($n = 1{,}859$).

	All patients % (n)	<65 yr % (n)	>65 yr % (n)	>70 yr % (n)	>75 yr %(n)
Number of individuals	100 (1,859)	57.7 (1,073)	42.3 (786)	21.5 (400)	12 (215)
ECOG					
0	33	36	29	24	23
1	67	64	71	76	77
2	0.2	0.1	0.3	0 (0)	0
Line of therapy on study (includes prior lines)					
1st line (after adjuvant or neo-adj)	1	0.6 (6)	1.4	1.6	0
2nd line	74	74	75	75	76
3rd line or greater	25	25.5	24	24	22
Smoking status					
Current/Former	82	81	83	83	86
Never	17.5	18	16.5	17	13
Unknown	0.5	0.7	0.4	0 (0)	0
Disease stage					
Not reported	0.9	0.8	0.9	1.3	0
Stage IIIB	11	10	11	11	6
Stage IV	78	79	76	78	94
CNS metastases					
Yes	13	16	9	7	5

PD-1 = programmed death 1 receptor; PD-L1 = programmed death ligand 1.

S. Marur et al. / Seminars in Oncology 000 (2018) 1–6

Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

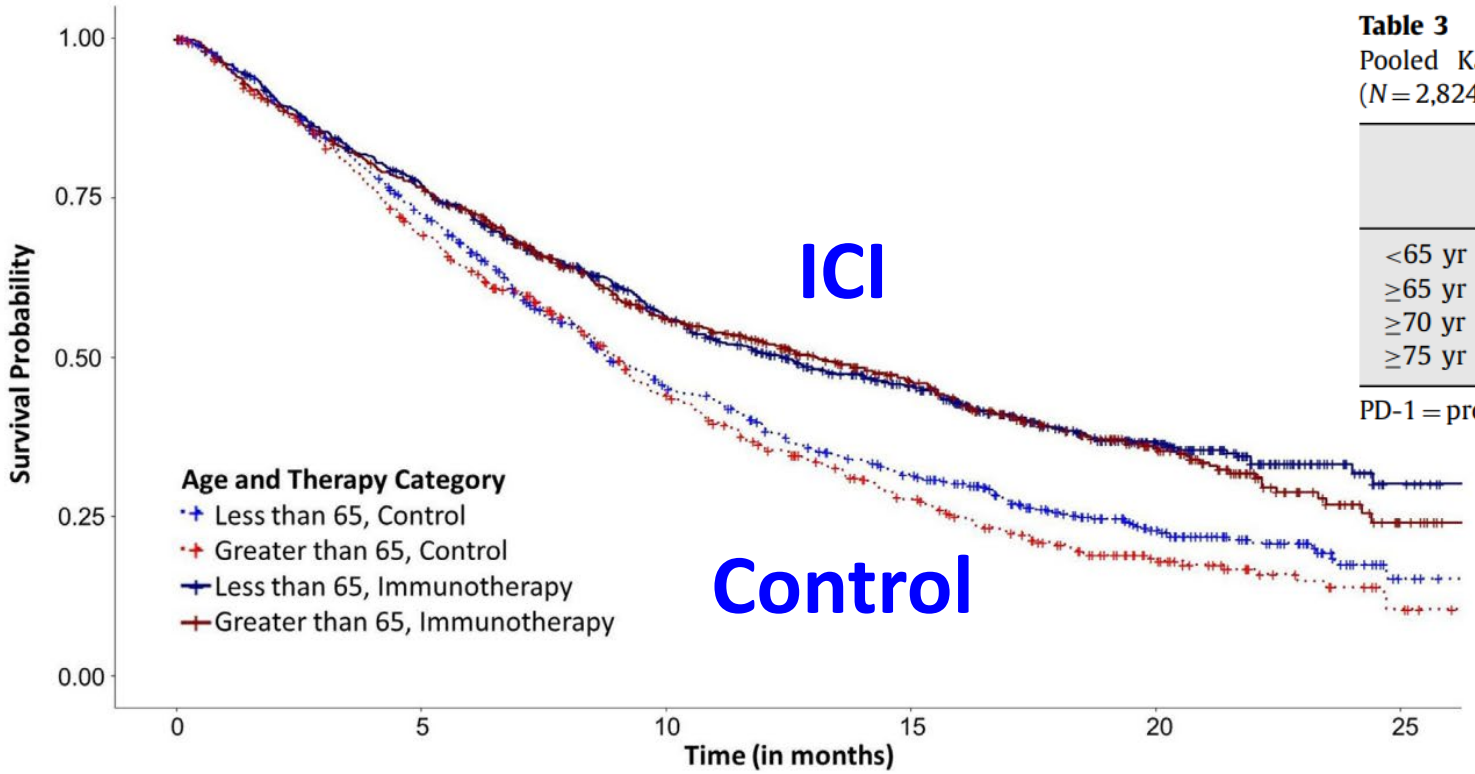


Table 3
Pooled Kaplan–Meier estimated median survival by treatment and age group ($N = 2,824$).

	PD-1/PD-L1 blocking antibodies			Docetaxel		
	N	Median (mo)	95% CI	*N*	Median (mo)	95% CI
<65 yr	921	14.5	(10.8, 14.2)	699	8.8	(8.3, 9.9)
≥65 yr	659	14.2	(11.0, 15.3)	545	9.0	(8.3, 9.6)
≥70 yr	300	14.1	(9.7, 15.0)	240	9.2	(8.2, 10.5)
≥75 yr	211	14.7	(9.1, 20.4)	149	9.5	(8.3, 15.5)

PD-1 = programmed death 1 receptor; PD-L1 = programmed death ligand 1.

S. Marur et al. / Seminars in Oncology 000 (2018) 1–6

Focus sul disegno degli studi clinici: Perché l'anziano è diverso dal paziente dei trial

Table 4
Overall survival hazard ratios (HR) from 4 trials comparing immune checkpoint inhibitors to docetaxel ($N = 2,824$).

	All patients ($N = 2,824$)	<65 ($N = 1,620$)	>65 ($N = 1,204$)	>70 ($N = 664$)	>75 ($N = 259$)
Hazard ratio (unadjusted)	0.68	0.71	0.66	0.67	0.81
95% CI	(0.63, 0.76)	(0.63, 0.80)	(0.57, 0.76)	(0.55, 0.82)	(0.58, 1.13)
Hazard ratio (multivar. adj.)*	0.68	0.69	0.66	0.67	0.81
95% CI	(0.62, 0.75)	(0.61, 0.79)	(0.58, 0.77)	(0.54, 0.82)	(0.58, 1.15)
Hazard ratio (age adjusted)**	0.68	0.69	0.66	0.67	0.81
95% CI	(0.62, 0.75)	(0.61, 0.79)	(0.58, 0.77)	(0.54, 0.82)	(0.57, 1.14)

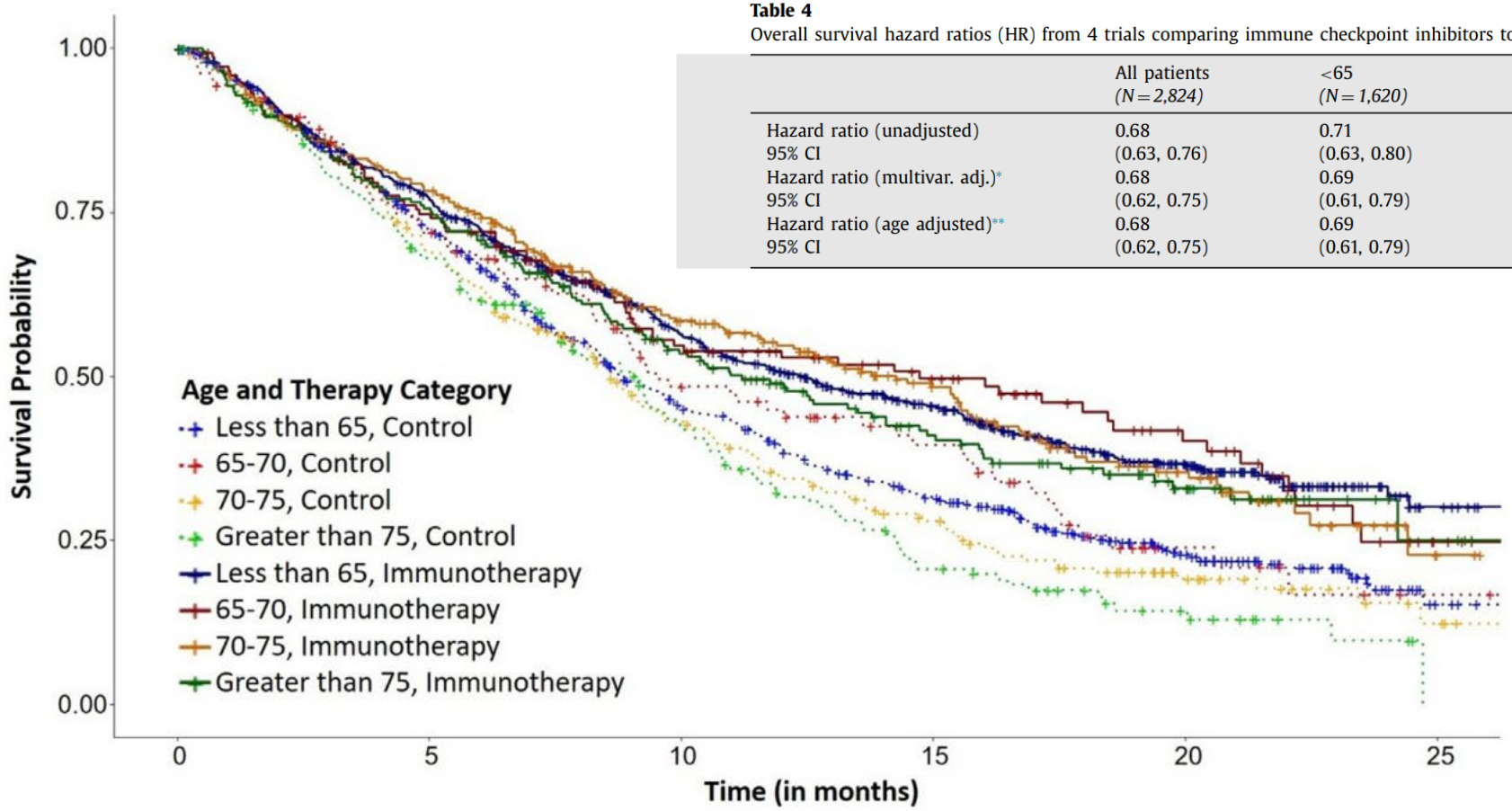


Fig. 3. Kaplan–Meier curves for overall survival by treatment and age subgroups in the pooled dataset ($N = 2,824$).

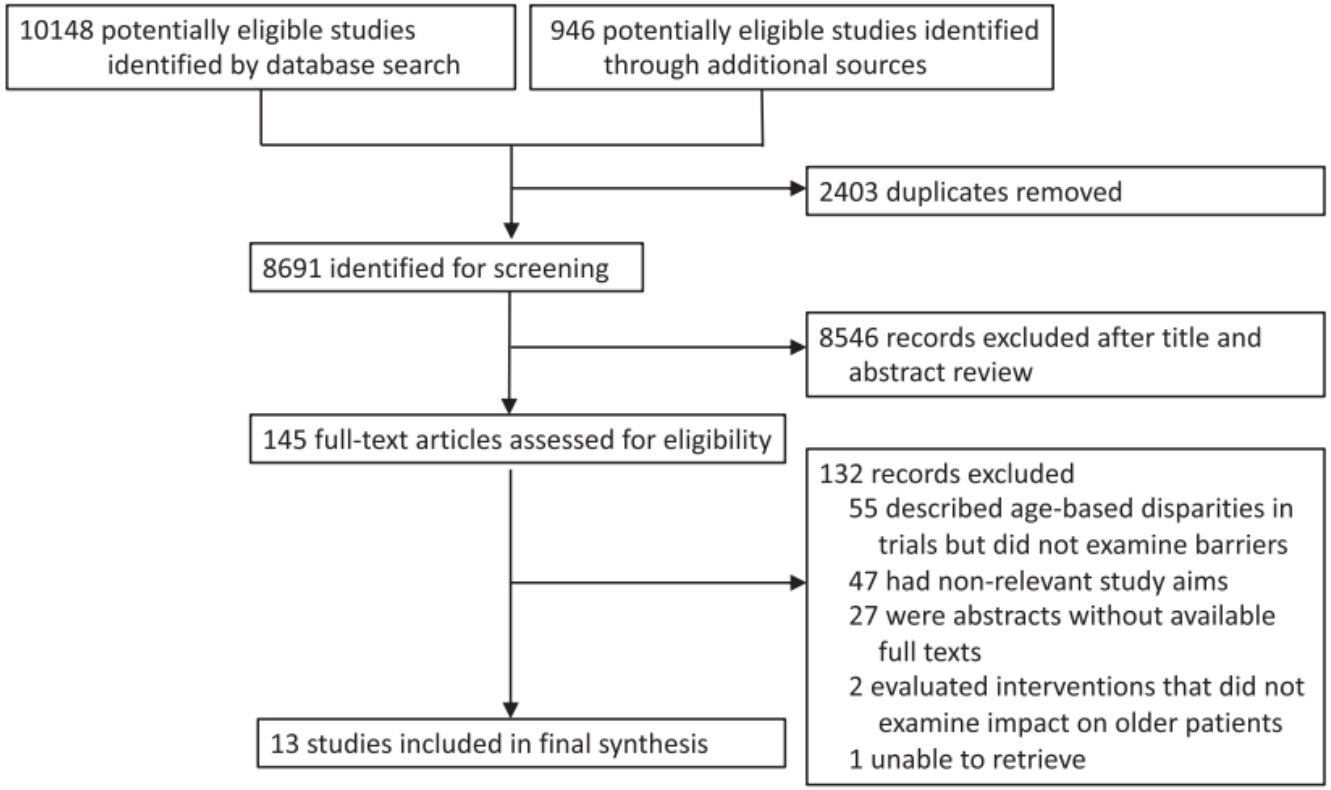
S. Marur et al. / Seminars in Oncology 000 (2018) 1–6

ICIs's rational – Immunosenescence

- Physiological deterioration of the immune system
- Lower effectiveness
- Risk of increased toxicity
- Available data from subgroup analyses, meta-analyses and retrospective studies
- Loss of benefit in OS >75 years
- Bias: not selected according to standardized geriatric scale; risk of underestimation of AEs.

Older adult patients and clinical trials

Older Adult Participation in Cancer Clinical Trials: A Systematic Review of Barriers and Interventions



CA CANCER J CLIN 2021;71:78–92

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

Older adult patients and clinical trials

Older Adult Participation in Cancer Clinical Trials: A Systematic Review of Barriers and Interventions

TABLE 1. Characteristics of the 13 Studies Included in This Systematic Review

CHARACTERISTIC	NO. OF STUDIES, N = 13	REFERENCES
Year published		
Before 2004	2	Kornblith 2002,[36] Kemeny 2003[69]
2004 to 2009	5	Townsley 2006,[37] Kimmick 2005,[42] Puts 2009,[70] Moore 2004,[71] Basche 2008[72]
After 2010	6	Javid 2012,[31] Freedman 2018,[38] Hamaker 2013,[73] Ayodel 2016,[74] McCleary 2018,[75] Prieske 2018[76]
Country of origin		
United States	8	Javid 2012,[31] Kornblith 2002,[36] Freedman 2018,[38] Kimmick 2005,[42] Kemeny 2003,[69] Puts 2009,[70] Moore 2004,[71] Basche 2008,[72] McCleary 2018[75]
Canada	2	Townsley 2006,[37] Puts 2009[70]
Netherlands	1	Hamaker 2013[73]
Ireland	1	Ayodel 2016[74]
Germany	1	Prieske 2018[76]
Minimum age used to define older adults		
65 y	11	Javid 2012,[31] Kornblith 2002,[36] Freedman 2018,[38] Kimmick 2005,[42] Kemeny 2003,[69] Puts 2009,[70] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] Ayodel 2016,[74] Prieske 2018[76]
70 y	2	Townsley 2006,[37] McCleary 2018[75]
Study population		
Provider	5	Kornblith 2002,[36] Freedman 2018,[38] Kimmick 2005,[42] Hamaker 2013,[73] McCleary 2018[75]
Patients	5	Townsley 2006,[37] Puts 2009,[70] Basche 2008,[72] Ayodel 2016,[74] Prieske 2018[76]
Both	3	Javid 2012,[31] Kemeny 2003,[69] Moore 2004[71]
Sample source		
Multiple institutions	9	Javid 2012,[31] Kornblith 2002,[36] Kimmick 2005,[42] Kemeny 2003,[69] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] McCleary 2018,[75] Prieske 2018[76]
Single institution	3	Townsley 2006,[37] Puts 2009,[70] Ayodel 2016[74]
Population-based	1	Freedman 2018[38]
Study design		
Intervention	1	Kimmick 2005[42]
Observation	12	Kornblith 2002,[36] Townsley 2006,[37] Freedman 2018,[38] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] Ayodel 2016,[74] McCleary 2018,[75] Prieske 2018[76]
Cross-sectional	9	Javid 2012,[31] Kornblith 2002,[36] Townsley 2006,[37] Freedman 2018,[38] Kemeny 2003,[69] Puts 2009,[70] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] Ayodel 2016,[74] McCleary 2018,[75] Prieske 2018[76]
Surveys	11	Javid 2012,[31] Kornblith 2002,[36] Townsley 2006,[37] Freedman 2018,[38] Kemeny 2003,[69] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] Ayodel 2016,[74] McCleary 2018,[75] Prieske 2018[76]
Qualitative analyses	4	Townsley 2006,[37] Kemeny 2003,[69] Puts 2009,[70] McCleary 2018[75]
Cohort	2	Javid 2012,[31] Puts 2009[70]
Case-control	1	Kemeny 2003[69]
Cancer type		
Solid	11	Javid 2012,[31] Kornblith 2002,[36] Townsley 2006,[37] Kemeny 2003,[69] Puts 2009,[70] Moore 2004,[71] Basche 2008,[72] Hamaker 2013,[73] Ayodel 2016,[74] McCleary 2018,[75] Prieske 2018[76]
Breast	6	Javid 2012,[31] Kornblith 2002,[36] Townsley 2006,[37] Kemeny 2003,[69] Hamaker 2013,[73] Ayodel 2016[74]
Colon	2	Townsley 2006,[37] McCleary 2018[75]
Lung	1	Townsley 2006[37]
Prostate	1	Townsley 2006[37]
Hematologic	3	Townsley 2006,[37] Basche 2008,[72] Ayodel 2016[74]
All types	2	Freedman 2018,[38] Kimmick 2005[42]

CA CANCER J CLIN 2021;71:78–92

Older adult patients and clinical trials

Older Adult Participation in Cancer Clinical Trials: A Systematic Review of Barriers and Interventions

Identified Barriers to Clinical Trial Participation of Older Adults With Cancer

- **System**
- **Provider**
- **Patient**
- **Caregiver**

BARRIER	REFERENCE											
	36	69	71	37	72	70	31	73	74	75	76	38
System												
Eligibility criteria	•		•				•	•		•		•
Consent form language							•	•				•
Trial availability			•									•
Provider												
Concern for toxicity	•	•	•				•	•		•		•
Concern for patient age	•						•	•		•		•
Time/burden	•						•	•		•		
Preference for another treatment	•	•						•				
Lack of personnel							•	•				•
Preference against research in general	•			•			•		•	•		
Unaware of available trials	•	•										
Patient												
Knowledge	•			•			•		•		•	•
Transportation	•				•		•		•		•	•
Time/burden					•	•	•	•			•	•
Concern about efficacy and toxicity				•	•	•	•		•		•	
Against experimentation	•	•			•		•	•				
Treatment preferences	•	•					•	•				
Finances	•				•		•					•
Age (eg, believing they are too old)				•					•			
Emotional burden						•						•
Caregiver												
Preferences	•			•			•					•
Burden	•						•					

CA CANCER J CLIN 2021;71:78–92

Older adult patients and clinical trials

Older Adult Participation in Cancer Clinical Trials: A Systematic Review of Barriers and Interventions

Recommendations to Expand the Inclusion of Older Adults in Cancer Clinical Trials

OVERARCHING SOLUTIONS	SPECIFIC STRATEGIES	EXAMPLES FOR IMPLEMENTATION
Operational modifications to the current cancer research infrastructure	Geriatricize trial design	• Design trials specifically for older adults (eg, single-arm phase 2 A171601)[a] • Extended trial design (no precedent) • Adaptative design (eg, phase 3 CALGB 49907)[b] • Prospective cohort design (eg, TLC study)[c] • Postmarketing surveillance cohorts/registries (eg, NRMI Genentech study)[d] • Embedded study (eg, A041202, EA2186)[e]
	Measure relevant endpoints	• Concurrent differential dosing trials (eg, FOCUS2, GO2)[f] • Composite endpoints (eg, *Overall Treatment Utility* or *Therapeutic Success*, which combines efficacy, toxicity, and patient compliance) • Treatment failure-free survival • Time to treatment failure • Patient-reported toxicity (eg, PRO-CTCAE) • Aging-related measures (eg, single or multiple domains of GA and other measures to capture function or cognition) • Quality-of-life–related measures (eg, PROMIS, EORTC, Q-TWIST) • Was It Worth It (WIWI) questionnaire
	Broaden (further) eligibility criteria	• Use measures of function (eg, gait speed) or other evaluations of biological age rather than performance status • Incorporate standardized, objective measures of multimorbidity, such as the Charlson Comorbidity Index (consider a hierarchy of comorbid conditions) • Engage (early) with patient advocates, geriatricians, or geriatric oncologists
	Address site/stakeholder-specific barriers	• Avoid shotgun, *one-size-fits-all* approach • Evaluate specific site and stakeholder barriers • Develop multilevel, tailored interventions to meet unique needs
Expand the reach of cancer and aging research beyond standard clinical trials	Design pragmatic clinical trials	• Consider cluster-randomized trials (eg, COACH trial)[g] • Expand to community-practices (eg, NCORP)
	Leverage real-world data	• Use EHRs, tumor registries, claims data, and other sources • Link cancer (eg, SEER) and aging data (eg, HRS)

CA CANCER J CLIN 2021;71:78–92

Inclusion of Older Adults in Cancer Clinical Trials Guidance for Industry

A. Early Clinical Development

B. Clinical Trials

C. Postmarket

- Sponsors should enroll older adults, if appropriate, in early phase studies to obtain information on safety, exposure, and response to better inform the study design and dose selection of later phase studies.
- Sponsors should evaluate drug interactions early in drug development to allow enrollment of older adults who may otherwise be excluded because of their concomitant medication use.
- Sponsors should document co-morbidities and make every effort to safely include these patients as well as those with organ dysfunction and prior/concurrent malignancies.[14]

U.S. Department of Health and Human Services Food and Drug Administration
Oncology Center of Excellence (OCE) Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER)
March 2022 Clinical/Medica

Inclusion of Older Adults in Cancer Clinical Trials Guidance for Industry

A. Early Clinical Developmen

B. Clinical Trials

C. Postmarket

- *Trial design*

  To facilitate the enrollment of older adults in cancer trials, sponsors may consider flexible approaches to trial design, such as age-based stratification or analyses based on hypothesized efficacy differences in older adults compared to the younger adults participants (≤65 years)… alternative trial designs should be proposed. This may include an open-label safety study that can enroll and analyze an older adult population separately in a parallel arm of a trial.

- *Develop recruitment strategies targeted to older adults*

  Clinical trials do not have an upper age limit for exclusion, however adults 75 years of age and older, continue to be underrepresented. FDA encourages sponsors and clinical trial cooperative groups to develop strategies to recruit patients that are reflective of the intended population.

- *Consider collecting additional information for older adults*

  For example, in addition to collection of age and performance status, elements from geriatric assessment tools (e.g. functional status, cognitive function), and a comprehensive assessment of comorbidities should be considered during trial design.

- *Consider additional strategies in adverse event monitoring and management*

- *Report more discrete age subgroups*

Inclusion of Older Adults in Cancer Clinical Trials Guidance for Industry

A. Early Clinical Developmen

B. Clinical Trials

C. Postmarket

Ideally, adequate information on older adults should be captured in the premarket clinical trials. However, if older adults are not adequately represented in premarket clinical trials, it may be appropriate to develop a plan to collect data on older adults in the postmarket setting

Conclusions (1)

- Older patients are significantly underrepresented in cancer clinical trials
- Exist complex and multifactorial barriers to enrolling older patients on cancer clinical trials
- Education and adequate information of patient and physician: very important!!
- Lack of data on tumor biology and treatment tolerance
- Cut off 70> 65 – 75>70?

Conclusions (2)

Is the elderly different from trial patients? Yes, but..

- Need for increase the enrolment of elderly patients
  - Modify trial design (stratification for age, I/E related to comorbidity, PS and pervious malignancy)
  - Embed biological or functional age evaluation in trials
  - Conduct concurrent differential dosing trials for older adults

Grazie per l’attenzione!