

Considerations and Challenges in
Treating Elderly Patients with Lung Cancer,
by Dr. Rogerio Lilenbaum



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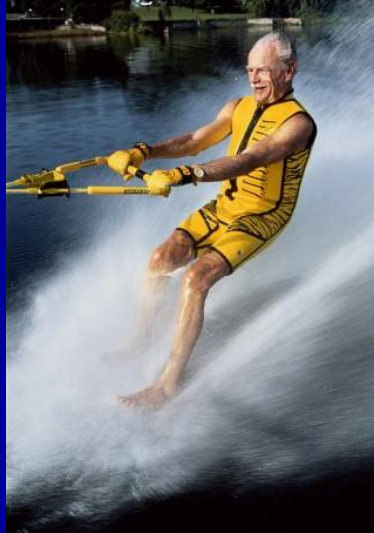


Elderly Patients with Lung Cancer

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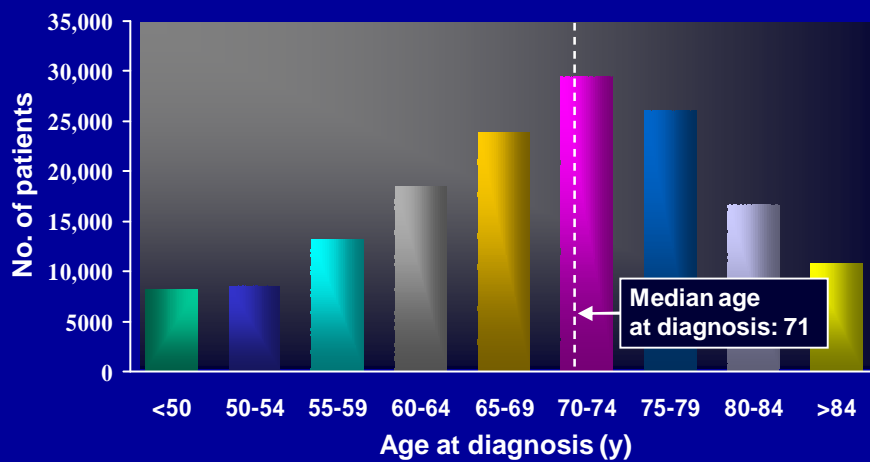


Chronological Age 80



Chronological Age Does Not Equal Functional Age

Incidence of NSCLC in the US by age at diagnosis



Data from SEER Cancer Statistics Review, 1975-2001.

Elderly Patients - Representation in Clinical Trials

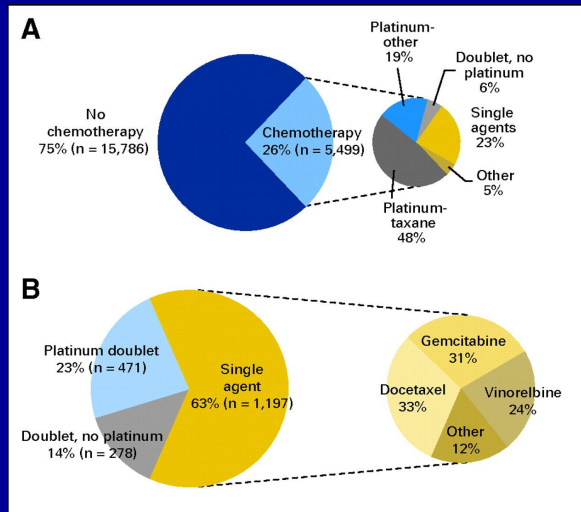
- 65% of lung cancer patients are ≥ 65
- 50% of lung cancer patients are ≥ 70
- Elderly representation on US Trials

<u>Study</u>	<u>% ≥ 70</u>
E5592	15%
S9509/9305	19%
E1594	20%
CALGB 9730	27%
ECOG 4599	26%

Elderly patients with Advanced NSCLC: Obstacles

- In clinical practice, elderly patients, often excluded from clinical trials, receive untested or inferior treatments, based on several long-held but undocumented beliefs:
 - Elderly have less aggressive cancers
 - Elderly do not want aggressive therapy
 - Elderly cannot tolerate aggressive therapy
 - Elderly have different wishes with respect to prolongation of life

Chemotherapy in patients aged 65 and more (SEER Database) between 1997 and 2002



A First-line
n = 21285
B : 2nd line
n = 2026

% pts receiving CT :
20.4% in 1997
27.8% in 2002

Davidoff A J et al. JCO 2010;28:2191-2197

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Elderly Patients with Advanced NSCLC

- From a clinician's perspective, the important considerations, when facing an elderly patient with advanced NSCLC, are the following:
 - Performance Status
 - Co-Morbidity
 - Overall Frailty
 - Patient's wishes and expectations

Geriatric Assessment: Functional Status Activities of Daily Living (ADLs)

Basic self-care skills

Dressing

Bathing

Toileting

Transfer

Continence

Eating

Geriatric Assessment: Functional Status Instrumental Activities of Daily Living

Higher order function

Required to maintain independence in the community

Shopping

Housekeeping

Transportation

Laundry

Telephone

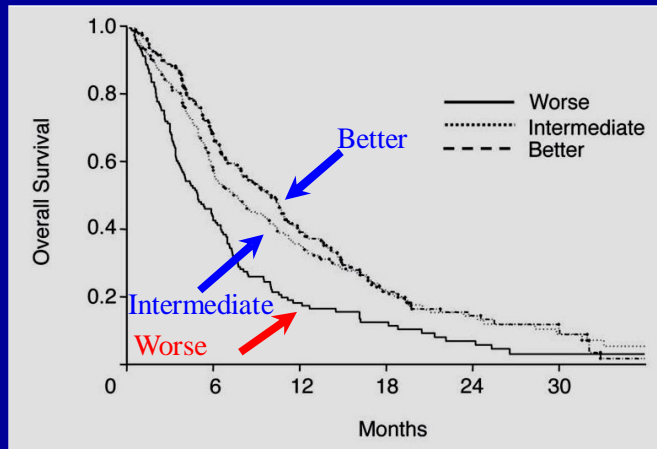
Finances

Medications

Assistance with IADLs → Worse Survival in Patients with Lung Cancer

Categories of IADLs:

- Better:
Score of 100%
- Intermediate:
Score of 51-99%
- Worse:
Score of 0-50%



Maione et al, J Clin Oncol, 2005

Co-morbidity

Definition:

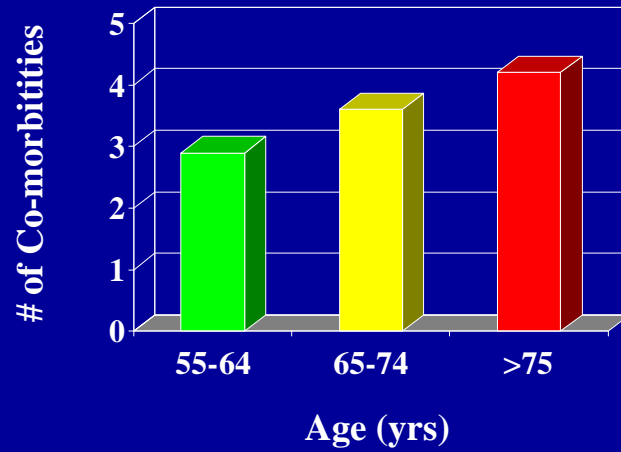
Concurrent, independent health condition which may be a predictor of survival and resource requirements

Questions:

- 1) Is the patient going to die from cancer or another medical problem?
- 2) Will another medical problem limit the ability to tolerate chemotherapy?

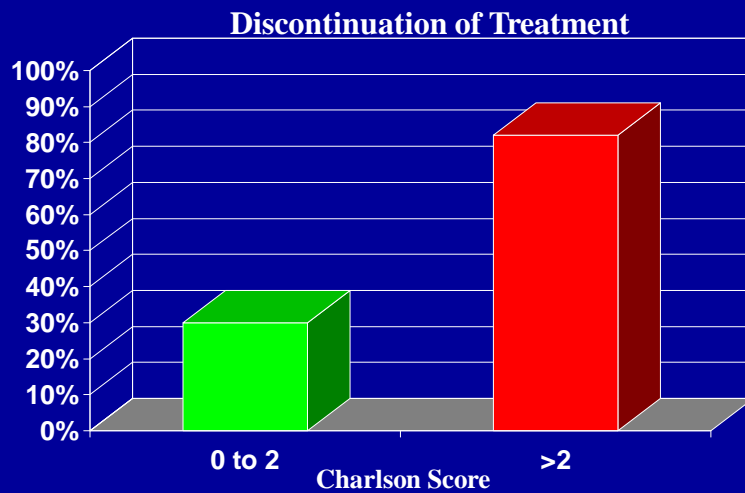
Courtesy of Dr. Hurria

Co-morbidity Increases with Age



Yancik et al, Cancer 1997

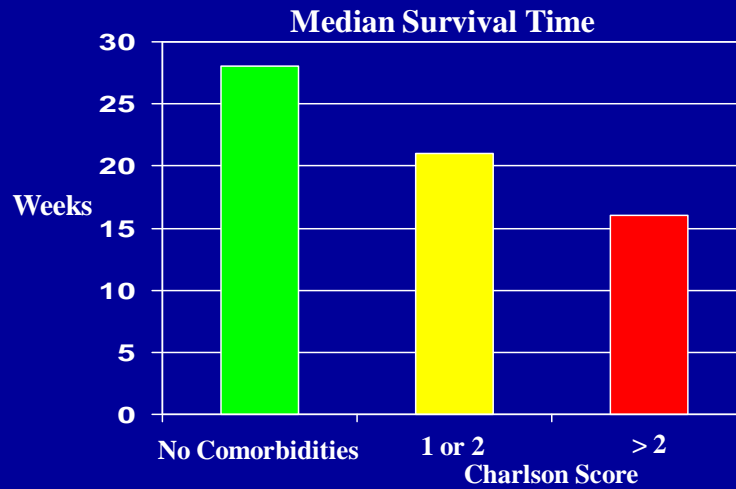
Increased Co-morbidity Correlates with Cancer Treatment Discontinuation



Higher co-morbidity score → more likely to discontinue treatment

Frasci et al, J Clin Oncol, 2000

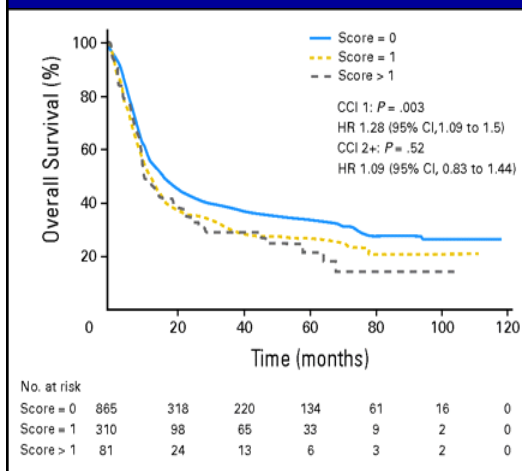
Co-morbidity → Decreased Survival in Patients with Lung Cancer



Higher co-morbidity score → worse survival

Frasci et al, J Clin Oncol, 2000

Age and Co-morbidity As Independent Prognostic Factors in NSCLC: A Review of NCIC



1,255 patients (774 advanced)

34% ≥ 65 years

31% with CCI ≥ 0

8% with PS 2

Age not prognostic for OS

CCI ≥ 1: poorer OS (HR
1.28; p = 0.003)

Asmis et al. JCO 2008

Adjuvant Chemotherapy: Trials vs. Reality

- Trials enroll young, fit patients
- Surgery compromises ability to get post-op chemo
- Many patients are hesitant, especially post-op
- Result: minority of early stage pts receive chemo, carbo/paclitaxel is leading regimen in US

Elderly Specific Analyses: BR10

Pepe et al ASCO '06, A-7009

- 65: designated cut-off
 - 327 younger pts (68 %)
 - 155 older pts (32 %)
- Baseline demographics similar except for histology and PS

Cohort	Younger	Older	P value
Adenoca	58%	43%	0.001
Squamous	32%	59%	0.001
PS 0	53%	42%	0.01

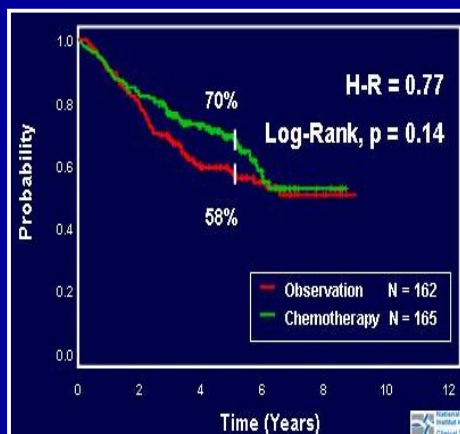
Elderly Specific Analyses - BR10: Survival

Pepe et al ASCO '06, A-7009

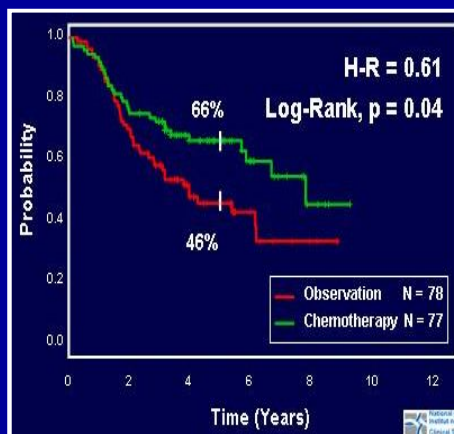
- Overall survival trended in favor of the young
 - Univariate analysis: HR 0.77; CI: 0.58-1.04, p=0.084
 - Multivariate analysis: HR 0.75; CI: 0.56-1.01, p=0.09
- Pts > 75 yrs: signif shorter survival vs 66-74
 - HR 1.95, CI: 1.11-3.41, p=0.02
 - But similar when corrected for disease-specific survival
- Chemotherapy statistically significant beneficial effect vs observation in the elderly
 - HR: 0.61, CI: 0.38-0.98, p=0.04

Overall Survival Benefit with Adjuvant Chemo, By Age

Age 65 and younger



Over 65



Pepe, PASC0 2006, A#7009; JCO 2007

RTOG 9410

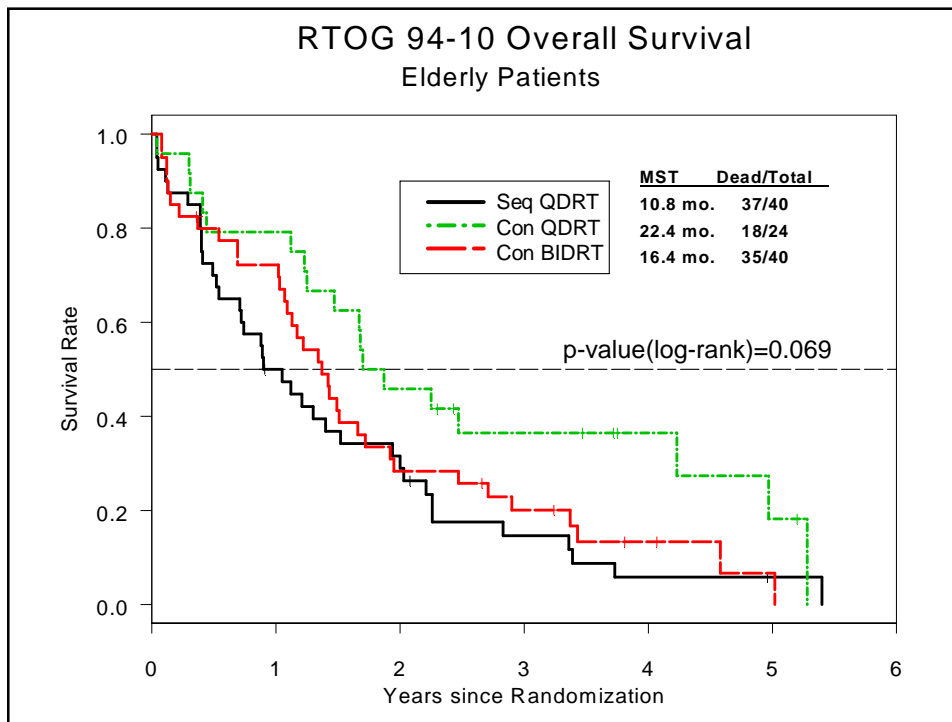
Langer et al. Proc Am Soc Clin Oncol. 2002; 21, 299a (abst 1193)

- Langer et al. re-evaluated patients ≥ 70 years who were enrolled in 94-10
- Eligible:
 - stage III NSCLC
 - good PS & Adequate pulmonary function
 - $< 5\%$ weight loss
- phase III trial:
 - sequential chemotherapy (cisplatin and vinblastine) & QDRT (sequential QDRT(60 Gy))
 - concurrent chemotherapy (cisplatin and vinblastine) & QDRT (concurrent QDRT(60 Gy))
 - concurrent chemotherapy (cisplatin and *etoposide*) & BIDRT (concurrent BIDRT (69.6 Gy))

RTOG 9410

Langer et al. ASCO 2002

- Of the 595 patients, 104 were ≥ 70 years
- Grade 3+ neutropenia and maximum toxicity per patient were more pronounced in elderly patients
- Of those patients who received concurrent therapy, grade 3+ esophagitis was 10-18% more common in the elderly patients (CON-QD: 33% vs. 23% & CON-BID: 60% vs. 42%)
- The median survival in the elderly patients was more favorable in those who received concurrent chemo plus RT
 - 22.4 months with concurrent QDRT
 - 16.4 months with concurrent BIDRT
 - 10.8 months for sequential QDRT ($p=0.069$)



Final Conclusions – Locally Advanced

- Elderly patients have similar survival rates as younger patients
- Additionally, “fit” elderly patients appeared to benefit from the more aggressive regimens (concurrent rather than sequential therapy or RT alone)
- Elderly patients experienced more myelosuppression
- Elderly patients also experienced greater non-hematologic toxicity: pneumonitis and esophagitis
- Future research should focus on decreasing treatment toxicity especially in the elderly
- Elderly-specific trials may help delineate better treatment approaches for these patients

Elderly Patients with Advanced NSCLC

- Multiple retrospective and prospective subset analyzes indicate that elderly patients (mostly between 70-75 years of age), with a PS 0-1, tend to fare as well as younger patients with carboplatin-based doublets in 1st line therapy

Elderly Patients with Advanced NSCLC

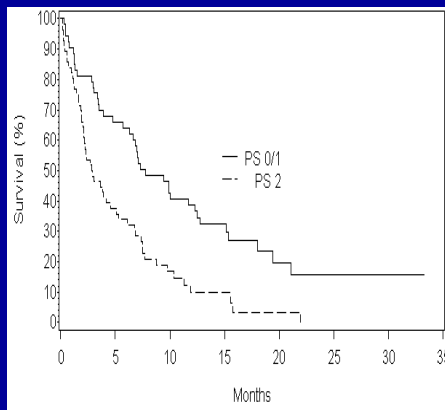
	MILES			Swedish		CALGB 9730	
	G	V	GV	G	CG	P	CP
Pts	233	233	232	65	56	78	77
ORR (%)	18.5	17.3	20	19	22	21	36
MST (mo)	9.2	7.0	7.8	9.4	11	5.8	8.0
1-Y Surv (%)	41	26	31	32	40	31	35

Gridelli et al. JNCI 2003; Sederholm et al. JCO 2006; Lilenbaum et al. JCO 2005

Elderly Patients with Advanced NSCLC

- Several clinical trials in elderly patients included PS 2 patients as a combined “special population” eligibility.
- These trials showed a distinct difference in outcome between age and PS

A Randomized Phase II Study of Two Schedules of Docetaxel in Elderly and PS 2 Patients with Advanced NSCLC – LUN 06

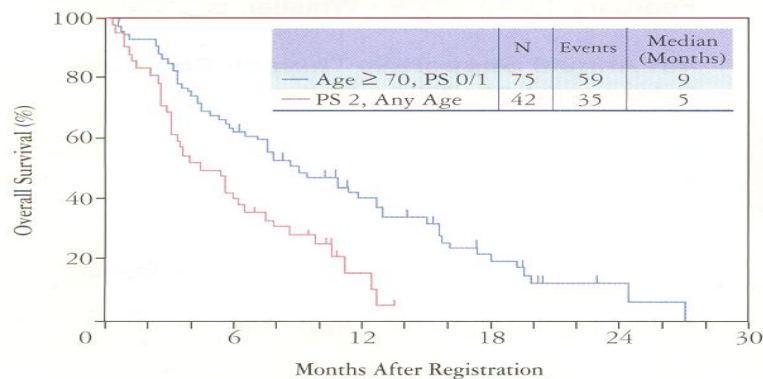


	PS 0-1 (n=47)	PS 2 (n=47)	<i>P</i> - <i>value</i>
Median TTP (mo)	3.1	1.6	0.043
Median Survival (mo)	7.9	2.9	<0.001

Lilenbaum et al. JTO 2007

SWOG Phase II Trial of Sequential Vinorelbine + Docetaxel in Elderly or Poor PS Patients with Advanced NSCLC

Figure 1 Overall Survival of Patients in SWOG 0027 Trial²



Overall survival for 75 eligible patients aged ≥ 70 with PS of 0/1 and 42 patients of any age with PS of 2.

Hesketh et al. JTO 2006

Elderly Patients with Advanced NSCLC

- There is little data regarding the efficacy and safety of biological agents in the elderly cohort

Outcomes for Elderly Advanced NSCLC Patients Treated With Bevacizumab in Combination with Carboplatin and Paclitaxel: Analysis of ECOG 4599 Study

	Elderly (≥ 70)*		Non-Elderly (< 70)	
	PC	PCB	PC	PCB
CR+PR	17%	29%	14%	36%
SD	50%	39%	50%	39%
Median PFS	4.9 m	5.9 m P=0.063	4.4 m	6.2 m P<0.001
1-Yr Survival	50%	46%	42%	53%
Median survival	12.1 m	11.3 m P = 0.4	9.6 m	12.8 m P = 0.0027

*Median Age "Elderly": 74

Ramalingam et al. JCO 2008

Toxicity on PCB Arm: Elderly vs. Non-Elderly

Grade 3/4	≥ 70 yrs	< 70 yrs	P
Neutropenia (Gr 4)	34%	22%	0.02
Melena/GI Bleed	3.5%	0.9%	0.005
Proteinuria	7.9%	1.3%	0.001
Motor neuropathy	3.5%	0.6%	0.05
Worst Grade	87%	70%	< 0.001
TRDs	6.3%	2.6%	0.08

Phase II study of Erlotinib in Advanced NSCLC Elderly Patients: Jackman et al., JCO 2007

No. Pts	80
Median Age	75 (70-91)
Female	50%
PS 2	10%
Adeno/BAC	64%
Never/Former Smokers	94%
PR – DCR	10% - 41%
TTP	3.5 months
MST	10.9 months

Rash and EGFR mutation
correlated with TTP and OS

12 patients removed for
toxicity (1 TD – ILD)

INVITE trial in advanced NSCLC elderly (>70 yrs) pts with PS ≤ 2

Arm	No	PS 2	DCR	TOI	PSI	Gr 3-5	ANC	Rash
VNR	99	16%	54	11	31	42%	44%	4%
GEF	97	24%	43	23	36	13%	0%	34%

*PSI – Pulmonary symptom improvement

HR for Gef vs Vnr

PFS: 1.19 (0.85, 1.69)

OS: 0.98 (0.66, 1.47)

HR for Vnr vs Gef for 54 FISH (+)

PFS: 3.13 (1.45, 6.73)

OS: 2.88 (1.21, 6.83)

Conclusions:

- Gefitinib and vinorelbine similar efficacy
- Gefitinib better tolerated
- Paradoxical benefit for VNR in FISH (+) pts

Crino et al IASLC '07

Crino L, Cappuzzo F, Zatloukal R et al. *J Clin Oncol*. 2008 Sep 10;26(26):4253-60

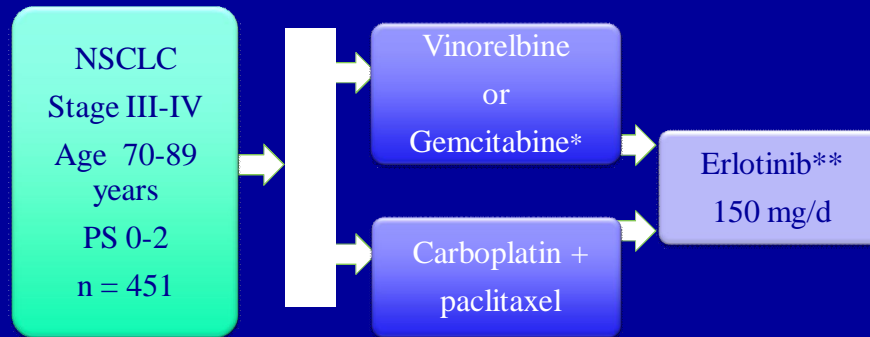
Elderly Patients with Advanced NSCLC

- There is a paucity of data for patients over the age of 75 and particularly over the age of 80. These patients tend to be managed with BSC or single-agent therapy

COMBINED RESULTS SWOG 0027 and LUN06

	SWOG 0027 patients < age 80	SWOG 0027 and LUN06 All patients ≥ age 80
Number of patients	94 (41.2%)	49 (21.5%)
Median age		82 (80-87)
PS 0-1/2		37/12
PR	16 (17%)	4 (8%)
SD	25 (27%)	22 (44.9%)
Median survival		
PS 0-1	11 months	7 months
PS 2	5 months	4 months
1-year survival		
PS 0-1	43%	32%
PS 2	15%	0%
Grade 2/4 toxicities	87/91 (96%)	38/49 (78%)

Weekly paclitaxel combined with carboplatin versus single agent therapy in patients aged 70 to 89 : IFCT- Randomized Phase III Study in Advanced NSCLC



Stratification by centre, PS 0-1 vs. 2, age ≤80 vs. >80 and stage III vs. IV

*Choice of the center at the beginning of the study

** In case of PD or excessive toxicity

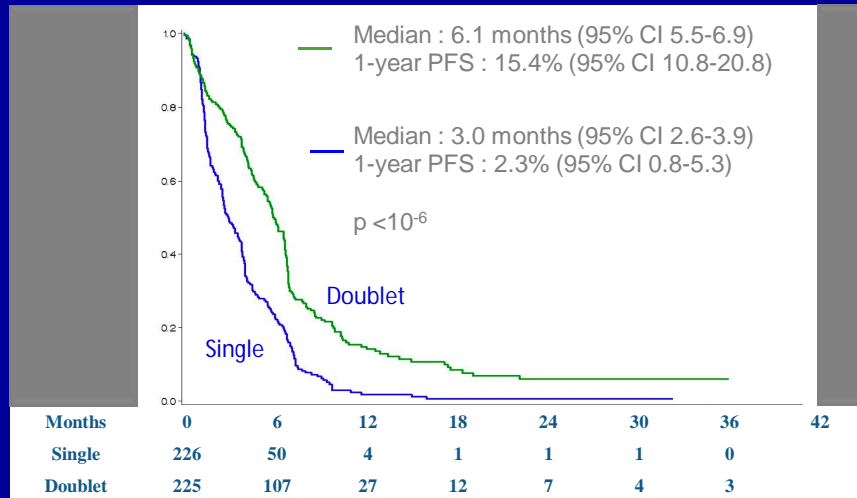
Quoix et al. ASCO 2010

Response rate at 6 weeks (ITT)

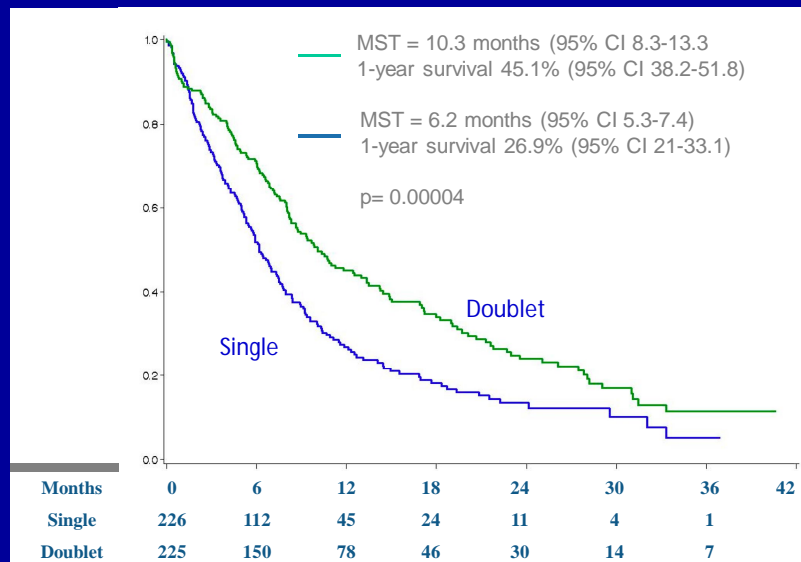
	Single Agent Arm A (n = 211)	Doublet Arm B (n = 210)	p
PR	23 (10.9%)	61 (29.05%)	<10 ⁻⁵
ST	96 (45.5%)	81 (38.57%)	0.18
DCR (PR + ST)	119 (56.4%)	142 (67.62%)	0.02
PD	46 (21.8%)	15 (7.14%)	<10 ⁻⁴
Not reported	15 (7.11%)	20 (9.53%)	0.47
Withdrawal before 1st evaluation*	31 (14.7%)	33 (15.7%)	0.88

*Main causes : deaths (20 in arm A and 23 in arm B), reduced general condition (respectively 7 and 4), toxicity 0 and 4 cases respectively and withdrawal of consent (6 cases)

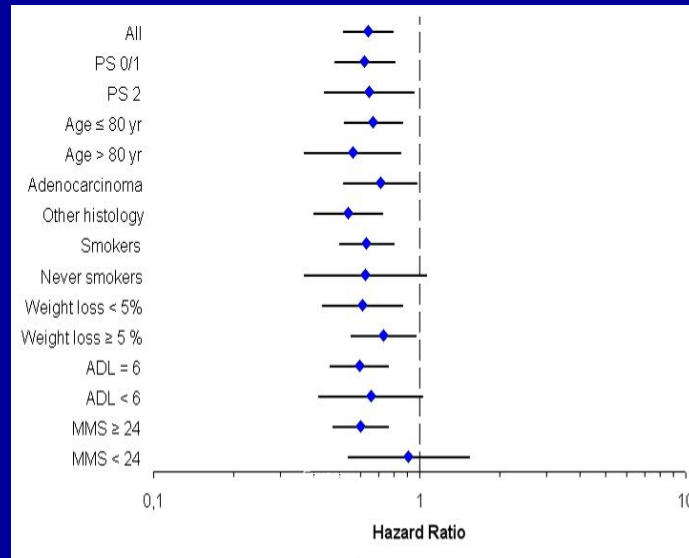
Progression-Free Survival (Intent to Treat)



Overall Survival (Intent to Treat)



Exploratory Sub-group analysis



Deaths

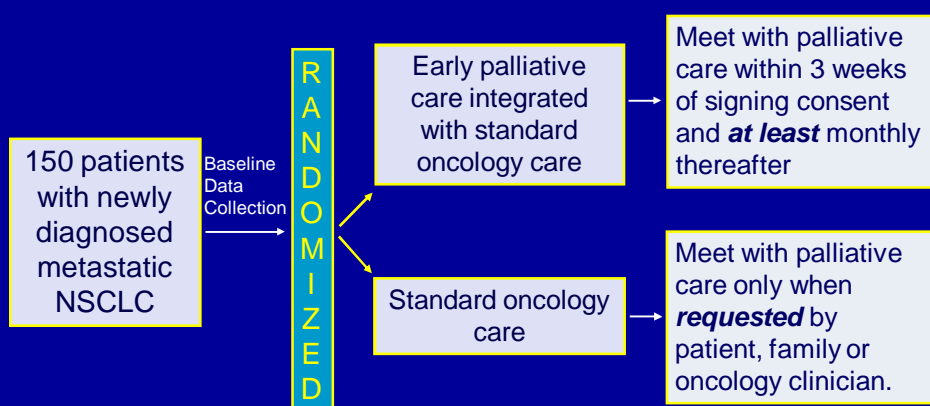
	Arm A single agent (n=168)	Arm B doublet (n=143)	p
Toxic deaths	3 (1.83%)	9 (6.62%)	0.035
Cancer	149 (90.90%)	112 (82.40%)	
Intercurrent disease	8 (4.88%)	14 (10.30%)	
Unknown	4 (2.44%)	1 (0.74%)	
Missing	4	7	

American Society of Clinical Oncology Treatment of Unresectable Non-Small-Cell Lung Cancer Guideline: Update 2003

David G. Pfister, David H. Johnson, Christopher G. Azzoli, William Sause, Thomas J. Smith, Sherman Baker Jr, Jemi Olak, Diane Stover, John R. Strawn, Andrew T. Turrisi, and Mark R. Somerfield

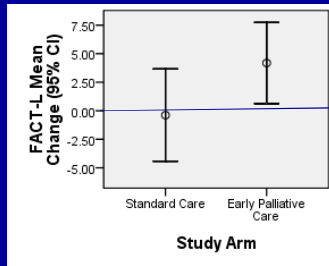
“For elderly patients or patients with ECOG/Zubrod performance status 2, available data support the use of single-agent chemotherapy”

EARLY PALLIATIVE CARE – ADVANCED NSCLC



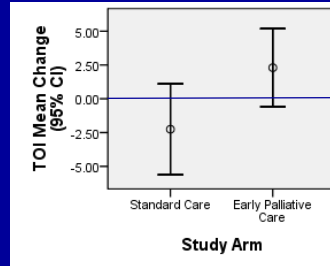
Change in QOL from Baseline to 12 Weeks

FACT-Lung



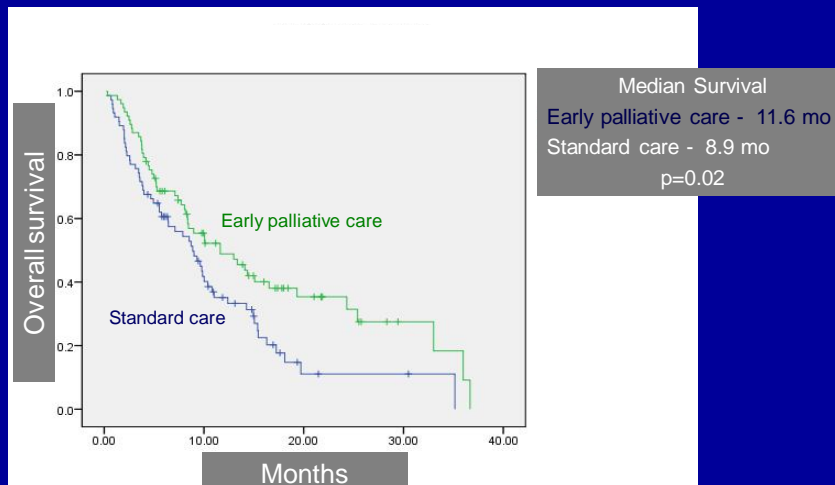
Mean change Early Palliative Care = + 4.2
 Mean change Standard Care = - 0.4
p=0.09

FACT- Lung TOI



Mean change Early Palliative Care = + 2.3
 Mean change Standard Care = - 2.3
p=0.04

Survival Analysis



Controlling for age, gender and PS, adjusted HR=0.59 (0.40-0.88), p=0.01

Elderly patients with Advanced NSCLC: Treatment Principles

- Age alone should not be a criterion for selection of therapy in advanced disease
- Dedicated chemotherapy trials in patients aged 70 to 75 with PS 0-1 are no longer necessary
- Dedicated studies are urgently needed in octogenarians
- Optimal use of targeted agents in elderly patients still a “moving target”
- Better assessment of co-morbidities and general “frailty index” is an important research goal



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