2016 NCCN CONGRESS SERIES™
National Comprehensive Cancer Network

LIVE WEBINARS

Treatment of Older Adult Patients with Non-Small Cell Lung Cancer

Presented by:

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Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and
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July 26, 2016

Moderated by Mark Geisler
NCCN, Conferences and Meetings Department

Supporters

- This activity is supported by educational grants from Ariad, AstraZeneca, Ethicon, Foundation Medicine, Genentech, Lilly, Novartis Pharmaceuticals Corporation, and Pfizer.
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Attendance Lists & Registration

- If you are participating with a group of peers, a list of everyone who attended in your group must be submitted within two weeks of the activity in order for the participants to be eligible to receive credit. This list is in addition to individual registration. Attendee lists will not be accepted after two weeks post-activity.
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Accreditation Information

Intended Audience

This educational program is designed to meet the educational needs of oncologists, nurses, pharmacists, and other health care professionals who manage patients with lung cancer.

Learning Objectives

Following this program, participants should be able to:

- Apply into practice tools--such as risk factor algorithm, frailty assessment, geriatric assessment, and performance status--to assess whether older patients with NSCLC can tolerate certain therapeutic interventions.
- Assess the risks and benefits of therapeutic interventions in the management of older patients with NSCLC who are at higher risk for adverse events from therapy.

Accreditation Information

Physicians

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Kristina M. Gregory, RN, MSN, OCN, is our lead nurse planner for this educational activity.

Accreditation Information

Pharmacists

Pharmacy Educational Objective: *After completing this activity, the participant should be able to:*

- Provide accurate and appropriate counsel as part of the treatment team.

Accreditation Statement

National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Type of Activity: Knowledge

UAN: 0836-0000-16-076-L01-P

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Accreditation Information

How to Claim Credit:

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Should you not receive an e-mail within 5 days, please contact us at **education@nccn.org.**

Accreditation Information

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    - There will be a separate WebEx evaluation at the conclusion of this program, which is optional and does not go to NCCN.
  - The follow-up post test (to be sent 30 days after the activity has ended to demonstrate an increase in participant competence)
- NCCN greatly appreciates your compliance with completing the aforementioned post-test and surveys. All of these measures will be available by logging into your account at **http://education.nccn.org**. Reminder e-mails will be sent to the participants via e-mail. If you have any questions or concerns, please e-mail **education@nccn.org**.

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All faculty for this continuing education activity are competent in the subject matter and qualified by experience, training, and/or preparation to the tasks and methods of delivery.

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The faculty listed below have disclosed the following relevant financial relationships:

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NCCN Staff Disclosures
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Ann Gianola, MA; Mark Geisler; Kristina M. Gregory, RN, MSN, OCN; Kristin Kline Hasson; Rose Joyce; Joan S. McClure, MS; Diane McPherson; Melanie Moletzsky; **Deborah Moonan, RN, BSN; Lisa Perfidio; Liz Rieder; Shannon K. Ryan; Kathy Smith; Jennifer McCann Weckesser**

The NCCN clinical information team listed below, who have reviewed content, has no relevant financial relationships to disclose:

Ellen Erkess; Kristina M. Gregory, RN, MSN, OCN; Miranda Hughes, PhD

Faculty Biography

Neelesh Sharma, MD, PhD, is Assistant Professor of Medical Oncology at University Hospitals of Case Comprehensive Cancer Center and Case Western Reserve University in Cleveland, OH.

Dr. Sharma earned his medical degree from G.S.V.M Medical College Kanpur in India and his doctorate of philosophy in pharmacology and toxicology from the University of Georgia. He completed a residency in internal medicine at the John H. Stroger, Jr. Hospital of Cook County and a fellowship in medical oncology at Roswell Park Cancer Institute, where he served as a Chief Fellow. He is board-certified in internal medicine, with a subspecialty in medical oncology.

Dr. Sharma specializes in the treatment of thoracic malignancies including lung cancer, mesothelioma and thymic cancer. His research interests include development of targeted therapies based on genomic alterations in lung cancer and early phase trials in developmental therapeutics program. He is studying how combination of novel drugs can circumvent or prevent emergence of acquired resistance to EGFR directed therapies.

Dr. Sharma is Principal Investigator (PI) or Co-PI for several ongoing clinical trials examining the efficacy of novel agents for the treatment of non-small cell lung cancer and other advanced malignancies. He is a member of various professional and scientific societies, including the Eastern Cooperative Oncology Group Thoracic Core Committee. He has authored and reviewed various scientific articles, abstracts, book chapters in prominent journals.

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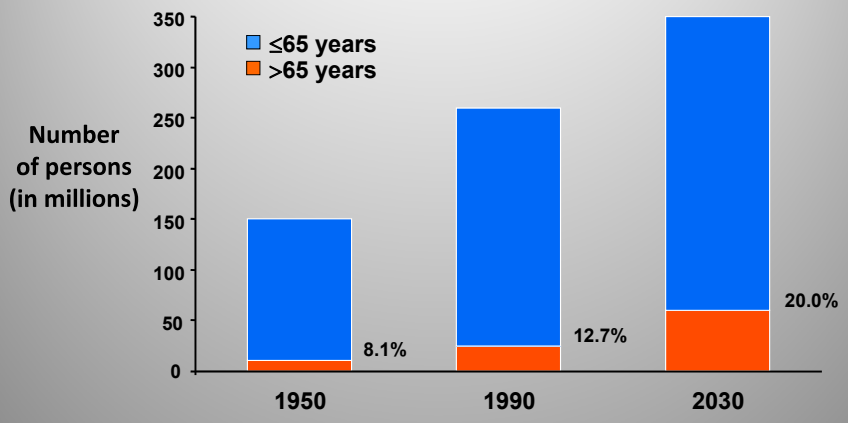
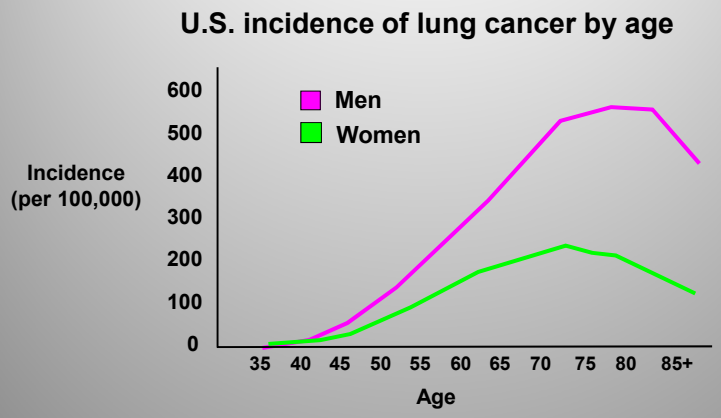
Neelesh Sharma, MD, PhD
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center

The U.S. Population Is Aging



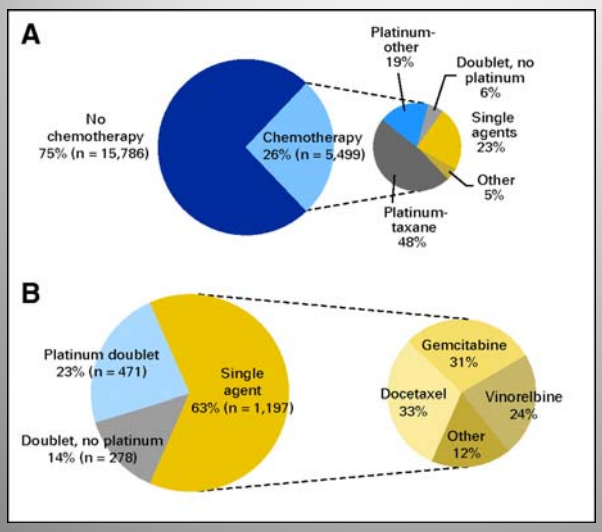
Yancik R, et al. *Hematol Oncol Clin North Am.* 2000;14:17–23.

Incidence of Lung Cancer Increases With Age



Yancik R, et al. *Comprehensive Geriatric Oncology.* 1998:95–104.

Chemotherapy in elderly patients (≥ 65) 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.

Elderly Lung Cancer Patients are Under-Represented on Clinical Trials

- 60% of lung cancer patients are ≥60
- 35% - 40% of lung cancer patients are ≥70
- Elderly representation on Trials

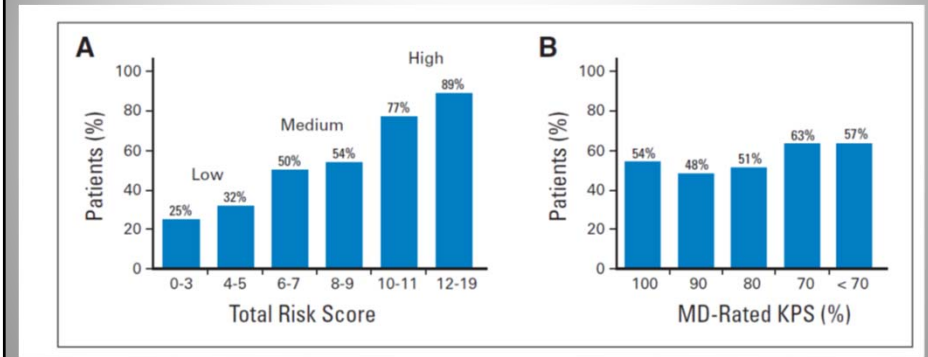
Study	% ≥70
E5592	15%
S9509/9305	19%
E1594	20%
CALGB 9730	27%
UNC	29%

CHALLENGES SPECIFIC TO ELDERLY PATIENTS
Heterogeneity in functional status
Age-related organ function decline
Alterations in Pharmacokinetics (excretion, metabolism, distribution and absorption)
Polypharmacy
Compromised immune responses
Lower marrow regenerative capacity
Comorbid conditions
Quality of life issues (in relation to life expectancy)

CARG (The Cancer and Aging Research Group) model for predicting chemotherapy toxicity in older adults

Age ≥72 years
Cancer type GI or GU
Chemotherapy dosing, standard dose
Number of chemotherapy drugs, polychemotherapy
Hemoglobin <11 g/dL (male), <10 g/dL (female)
Creatinine clearance (Jelliffe, ideal weight) <34 mL/min
Hearing, fair or worse
Number of falls in last six months, one or more
IADL (instrumental activities of daily living): Taking medications, with some help/unable
MOS (Medical Outcomes Study): Walking one block, somewhat limited/limited a lot
MOS: Decreased social activity because of physical/emotional health, limited at least sometimes

Arti Hurria et al. J Clin Oncol 2011, 29:3457-3465



Ability of (A) risk score versus (B) physician-rated Karnofsky performance status (KPS) to predict chemotherapy toxicity.

Arti Hurria et al. J Clin Oncol 2011, 29:3457-3465.

Patient is 85 year old female with newly diagnosed lung adenocarcinoma with mets to liver and bones. Negative for EGFR mutation, ALK or ROS-1 rearrangement. She has ECOG performance status of 1 and no significant co-morbidities.

What would be the best approach for first line treatment?

1. Supportive Care Only
2. Single agent Vinorelbine
3. Single agent Gemcitabine
4. Carboplatin and Pemetrexed
5. Carboplatin, Paclitaxel and Bevacizumab

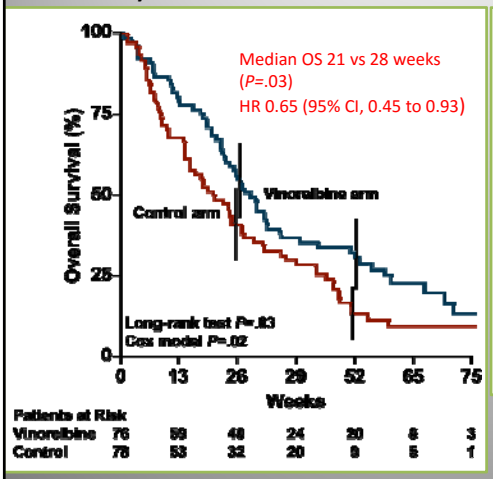
Treatment of Elderly Patients with Metastatic NSCLC

- Is chemotherapy better than best supportive care?
- Platinum based therapy or non-platinum?
- Single agent vs doublet?
- Bevacizumab or not?
- Other targeted agents?

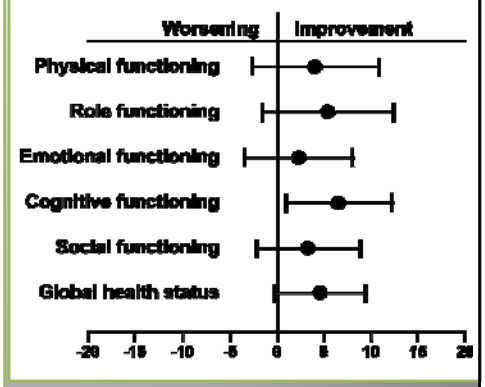
The Elderly Lung Cancer Vinorelbine Italian Study (ELVIS): Chemo vs BSC.

Vinorelbine 30 mg/m^2 days 1 & 8 every 21 days vs supportive care

1-year Survival 14% vs 32%



Favorable QoL Overall



ELVIS Group. *J Natl Cancer Inst*. 1999;91:66-72.

The MILES phase III trial: gemcitabine + vinorelbine vs vinorelbine vs gemcitabine in elderly advanced NSCLC patients

NSCLC

70+ years old

Chemotherapy naïve

Stage IIIB or IV

PS 0-2

RANDOMIZE

- vinorelbine 30 mg/m^2 d1,8 Q 3 weeks
- gemcitabine 1200 mg/m^2 d1,8 Q 3 weeks
- gemcitabine 1000 mg/m^2 d1,8 vinorelbine 25 mg/m^2 d1,8 Q 3 weeks

Cesare Gridelli *et al.* JNCI 2003 Vol. 95, N0 5

ITT Analysis of Efficacy

	VNR	GEM	VNR+GEM
No of patients (n)	233	233	232
Stage IIIB (%)	29	30	31
Response rate (%)	18	16	21
Time to Progression (wk)	18	17	19
Median Survival (weeks)	36 (30-45)	28 (25-34)	30 (27-36) HR 1.17 (vs VNR) HR 1.06 (vs GEM)
1 yr survival (%)	41%	26%	31%

Cesare Gridelli *et al.* JNCI 2003 Vol. 95, N0 5.

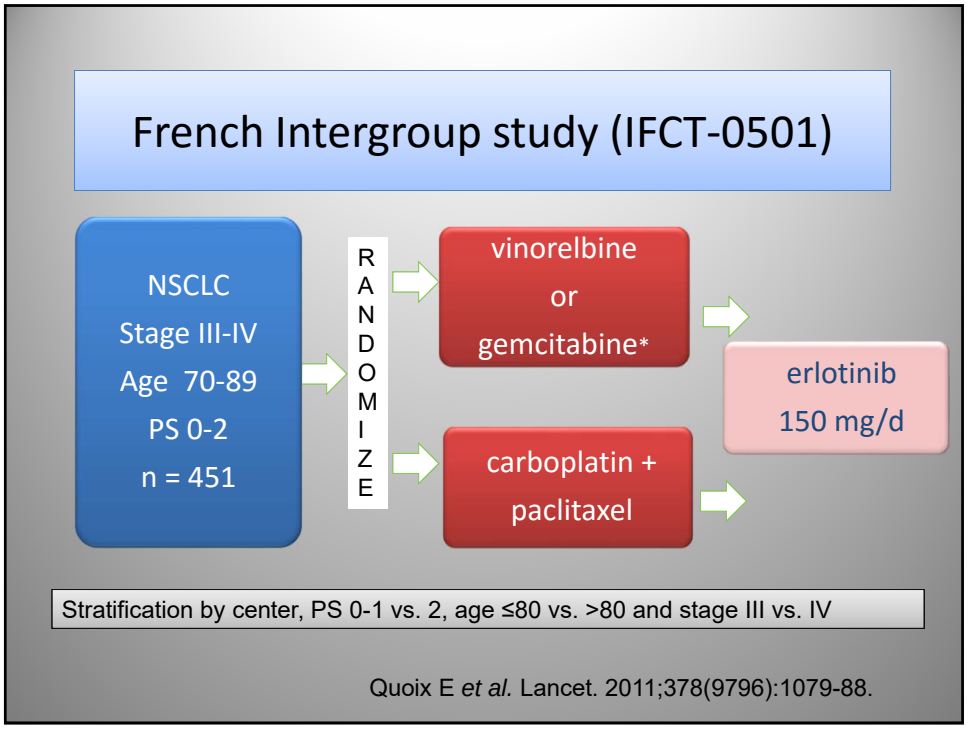
ECOG 5592: Elderly Data

- Patients randomized to cisplatin 75 mg/m^2 &
  - etoposide 100 mg/m^2 d 1-3
  - paclitaxel 135 mg/m^2
  - paclitaxel 250 mg/m^2 + G-CSF
- BREAKDOWN by Elderly (≥ 70) v "Young" (<70)
  - Elderly: ↑ cardiovascular (p=0.0089) + resp (p=0.0441) co-morbidities

Age	N	RR (%)	TTP (mo)	MS (mo)	1 YS (%)	2 YS (%)
<70	488	21.5	4.37	9.05	38	14
≥70	86	23.3	4.30	8.53	28	12
P value		0.666	0.294	Log rank 0.2857		

  - ↑ leukopenia (p=0.0001) and neuropsych tox (0.0025) in ≥ 70 yrs
  - No difference baseline QoL, Trial outcome index

Langer et al., *JNCI* 94(3): 173-181, 2002.



Progression Free Survival (PFS)

- **Doublet chemotherapy**
  - Median PFS: **6.1** months (95% CI 5.5-6.9)
  - 1-year PFS: 15.4% (95% CI 10.8-20.8)
- **Monotherapy**
  - Median PFS: **3.0** months (95% CI 2.6-3.9)
  - 1-year PFS: 2.3% (95% CI 0.8-5.3)

Quoix E *et al.* Lancet. 2011;378(9796):1079-88.

Overall Survival (OS)

- **Doublet chemotherapy**
  - Median OS = **10.3** months (95% CI 8.3-13.3)
  - 1-year survival 45.1% (95% CI 38.2-51.8)
- **Monotherapy**
  - Median OS = **6.2** months (95% CI 5.3-7.4)
  - 1-year survival 26.9% (95% CI 21-33.1)

Quoix E *et al.* Lancet. 2011;378(9796):1079-88.

Adverse Events

- Overall well tolerated
- Grade 3 or 4 neutropenia was more common with the combination compared with monotherapy (48 versus 12 percent).
- Ten deaths (4.4 percent) in the combination arm were attributed to treatment, compared with three (1.3 percent) in the monotherapy group.

Quoix E *et al.* Lancet. 2011;378(9796):1079-88.

Carbo/paclitaxel vs. carbo/nab-paclitaxel

Stage IIIb/IV NSCLC
No prior treatment for metastatic disease
PS 0-1
N = 1,050

Patients had no active brain metastases or ≥ grade 2 neuropathy at baseline

1:1

albumin-bound paclitaxel
100 mg/m² d1, 8, 15
carboplatin AUC 6 d1
21 Day Cycles

No Premedication

paclitaxel 200 mg/m² d1
carboplatin AUC 6 d1
21 Day Cycles

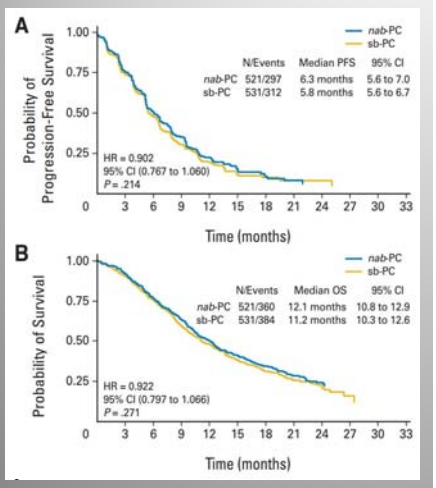
With Premedication of dexamethasone + antihistamines

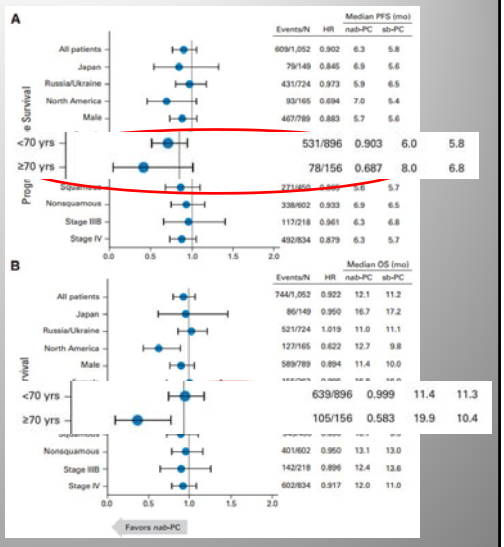
Patient Characteristics

	ab-P/C (n=521)	P/C (n=531)	All Patients (N=1052)
Age, median (range) years	60 (28, 81)	60 (24, 84)	60 (24, 84)
<65 years, n (%)	360 (69)	348 (66)	708 (67)
≥65 years, n (%)	161 (31)	183 (34)	344 (33)

Socinski, et al. 2010 ASCO LBA7511

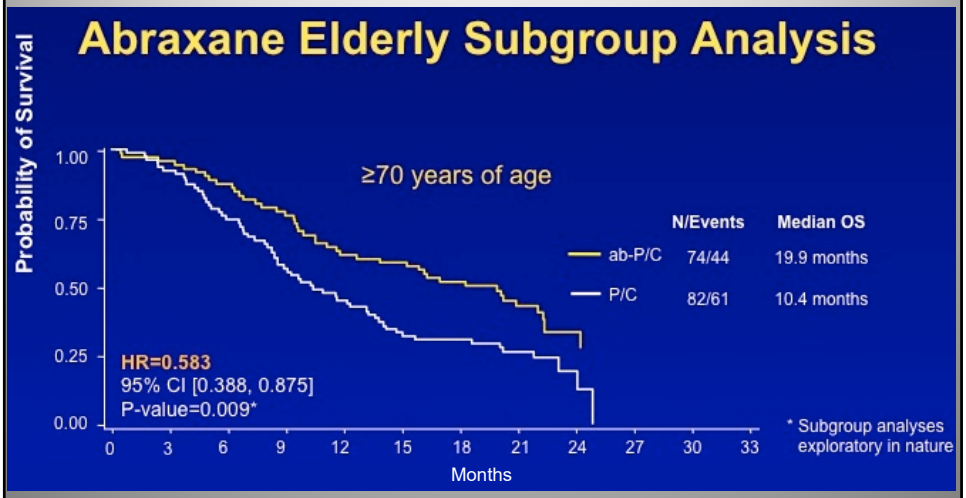
Carbo/paclitaxel vs. carbo/nab-paclitaxel





Socinski, et al. JCO 30:17, 2012

Overall Survival



Socinski et al, ASCO 2011, Abstr 7551

Ongoing prospective studies of nab-paclitaxel for elderly patients with NSCLC

Trial ID	Title	Treatment	Primary Outcome
NCT02151149	Phase IV study of nab-paclitaxel (A) in Combination With carboplatin (C) as First Line Treatment in Elderly Subjects With Advanced NSCLC (Abound.70+)	Arm A: A 100 mg/m2 IV on Days 1, 8, and 15 and C AUC = 6 every 21-day Arm B: A 100 mg/m2 IV on Days 1, 8, and 15 and C AUC = 6 every 28-day	Peripheral neuropathy or myelosuppression
NCT01702844	Phase II, single arm Study of the tolerability of weekly A as second line treatment for elderly patients with NSCLC	A 100 mg/m2 IV on Days 1, 8, and 15 every 28 days	Grade 3 or worse toxicity after 6 cycles or 3 weeks after discontinuation of treatment
NCT02590003	A Randomized Phase II Trial of Combination Versus Single Agent Chemotherapy in High-risk Elderly Patients With Advanced NSCLC	Arm A: A 100 mg/m2 IV on Days 1 and 8 and C AUC = 5 every 21-day Arm B: A 100 mg/m2 IV on Days 1 and 8 every 21-day	Progression Free Survival

Cis/pem vs. cis/gem elderly data (Nonsquamous patients)

Toxicity	Age < 65 Years n = 815 (67.2%)		Age ≥ 65 Years n = 398 (32.8%)	
	Pem + Cis (n = 390)	Gem + Cis (n = 425)	Pem + Cis (n = 215)	Gem + Cis (n = 183)
Thrombocytopenia	11 (2.8)	34 (8.0)	11 (5.1)	32 (17.5)
Neutropenia	45 (11.5)	107 (25.2)	45 (20.9)	49 (26.8)
Anemia	23 (5.9)	43 (10.1)	7 (3.3)	19 (10.4)
Leukopenia	15 (3.8)	34 (8.0)	11 (5.1)	12 (6.6)
Diarrhea Without Colostomy	6 (1.5)	5 (1.2)	1 (0.5)	4 (2.2)
Fatigue	26 (6.7)	15 (3.5)	14 (6.5)	12 (6.6)
Febrile Neutropenia	2 (0.5)	12 (2.8)	6 (2.8)	8 (4.4)
Nausea	32 (8.2)	17 (4.0)	17 (7.9)	10 (5.5)
Vomiting	27 (6.9)	29 (6.8)	11 (5.1)	9 (4.9)

HR OS (all favor pem):

Subgroup <65: .0.89
Subgroup ≥65: .0.75

Subgroup <70: .0.83
Subgroup ≥70: .0.85

Gridelli et al, Clinical Lung Cancer, 13:5, 2012.

JMEN elderly data: pem vs. placebo

Toxicity	Age < 65 Years n = 319 (67%)		Age ≥ 65 Years n = 157 (33%)	
	Pem (n = 217)	Placebo (n = 102)	Pem (n = 103)	Placebo (n = 54)
Neutropenia	6 (2.7)	0	3 (2.9)	0
Anemia	4 (1.8)	0	4 (3.8)	0
Fatigue	6 (2.7)	0	7 (6.7)	1 (1.9)
Neuropathy: Sensory	1 (0.5)	0	2 (1.9)	0
Constipation	1 (0.5)	0	0	1 (1.9)
Distention/Bloating, Abdominal	1 (0.5)	0	0	1 (1.9)

HR OS (all favor pem):

Subgroup <65: .0.62
Subgroup ≥65: .0.87

Subgroup <70: .0.63
Subgroup ≥70: .0.81

Gridelli et al, Clinical Lung Cancer, 13:5, 2012.

Treatment Scheme of ECOG 4599

Non-squamous NSCLC

Absence of brain metastasis

ECOG PS 0 or 1

Informed consent

RANDOMIZE

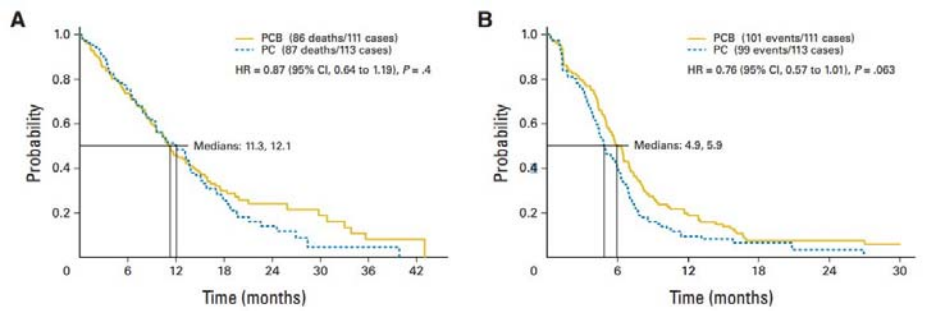
carboplatin (AUC 6)
paclitaxel 200 mg/m2
bevacizumab 15 mg/kg*

carboplatin (AUC 6)
paclitaxel 200 mg/m2

* Bevacizumab continued as monotherapy for CR/PR/SD after 6 cycles

Ramalingam, JCO 26:1, 2008

Subset Analysis of ECOG 4599: Elderly patients treated with bevacizumab in combination with carboplatin and paclitaxel



Ramalingam et al. J Clin Oncol. 2008 Jan 1;26(1):60-5

Safety in E4599

Incidence of gr 3–5 AEs was significantly higher for PCB vs. PC alone

Age	PC + Bev	PC
Grade 3–5 toxicity[a] <75 years	63%	48%
Grade 3–5 toxicity[a] ≥75 years	81%	56%
Grade 5 toxicity ≥75 years	8%	2%

[a]*P* <.005

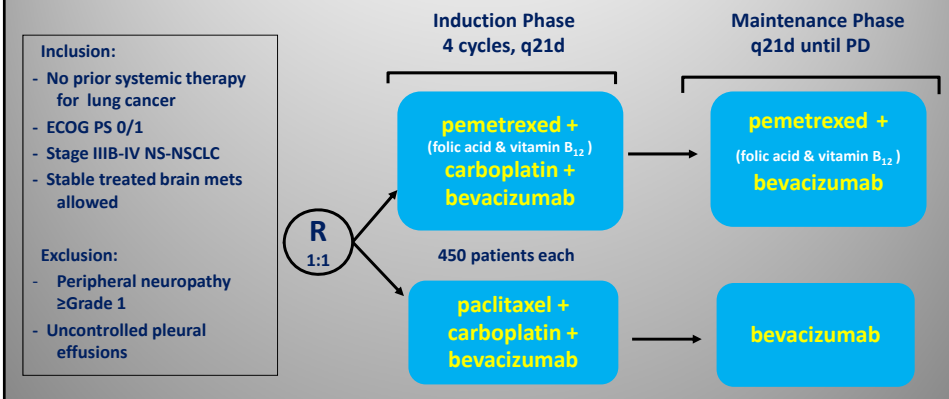
Rates for discontinuations due to AEs also higher for PC + Bev vs. PC alone

Age	PC + Bev	PC
<75 years	17% (65/375)	12% (49/401)
≥75 years	29% (17/59)	19% (8/43)

Ramalingam et al. J Clin Oncol. 2008 Jan 1;26(1):60-5

PointBreak

- **Randomized, open-label, phase III superiority study**
- **pemetrexed 500 mg/m²; carboplatin AUC 6; bevacizumab 15 mg/kg**
- **paclitaxel 200 mg/m²; carboplatin AUC 6; bevacizumab 15 mg/kg**



Primary Endpoint: Overall Survival

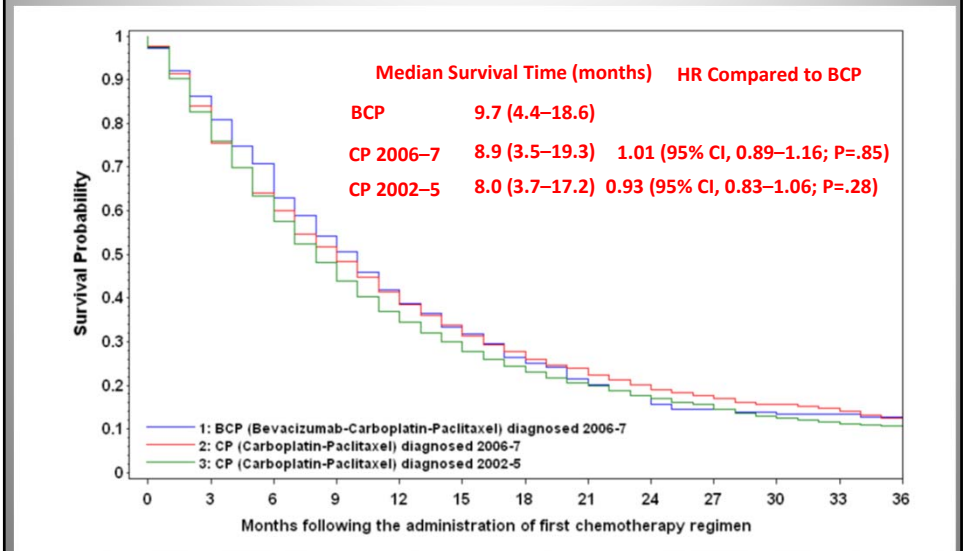
Socinski M, et al. ASCO 2013

Pooled analysis of Phase III E4599 and Point Break Randomized Clinical Trials Treatment: Avastin + PC vs. PC	Age 65-74	Bevacizumab + PC vs. PC: ❖ OS: HR 0.80 (0.64-1.00) ❖ PFS: HR 0.62 (0.49-0.78)
	Age 65-74	❖ OS: HR 0.68 (0.48-0.96) ❖ PFS: HR 0.57 (0.40-0.81)
	Age <75	❖ OS: HR 0.78 (0.68-0.89) ❖ PFS: HR 0.69 (0.60-0.79)
	Age ≥75	❖ OS: HR 1.05 (0.70-1.57) ❖ PFS: HR 0.95 (0.62-1.44)

PC: paclitaxel and carboplatin

Langer *et al.* Am J Clin Oncol. 2015

Retrospective cohort study of Medicare beneficiaries



Junya Zhu et al. JAMA. 2012 April 18; 307(15): 1593–1601.

Patient is 82 year old male with T3N1 M0 lung adenocarcinoma, s/p right lower lobectomy and mediastinal nodal dissection. Patient has recovered well from surgery and has ECOG performance status of 0 with no significant co-morbidities.

What would be the appropriate adjuvant chemotherapy?

A. No need for adjuvant chemotherapy
B. Cisplatin and Vinorelbine
C. Carboplatin and Paclitaxel
D. Cisplatin, Vinorelbine and Bevacizumab

Adjuvant Chemotherapy

- The standard for patients with stages IB to IIIA (high-risk) NSCLC is postoperative cisplatin-based combination chemotherapy for four cycles.
- The LACE (Lung Adjuvant Cisplatin Evaluation) meta-analysis reviewed all five cisplatin-containing trials with 4,584 patients; that study reported an overall survival benefit of 5.4% at 5 years.

Pignon JP *et al.* J Clin Oncol 2008;26(21):3552-3559.

An age-based analysis of the LACE data

- An age-based analysis of the LACE data showed no difference in survival among the age groups of younger than 65 (n=3269), 65 to 70 (901) and older than 70 years (n=414).
- Elderly patients received significantly lower cisplatin doses and fewer chemotherapy cycles.
- Rates of severe toxicity were comparable between groups.

Martin Früh et al. J Clin Oncol 2008, 26:3573-3581.

Ontario Cancer Registry Data

- Outcome of elderly (≥70 years) patients (n=2763) treated before (2001–2003) or after (2004–2006) the adoption of adjuvant chemotherapy.
- The cisplatin/vinorelbine combination was the most frequently used doublet across all age groups.
- Adjuvant chemotherapy administration was associated with a significant survival benefit in the elderly (although not for patients older than 80 years, n = 282) with tolerability similar to that of patients <70 years.

Sinead Cuffe et al. J Clin Oncol 2012, 30:1813-1821.

- Wisnivesky *et al.* reported the data from SEER database for 3,324 patients who were 65 years of age or older. No survival advantage was observed in patients older than age 80 years (HR, 1.33; 95% CI, 0.86 to 2.06).

- Comparison of carbo vs cisplatin based adjuvant chemotherapy in SEER-Medicare database showed comparable OS benefit and a slightly better toxicity profile.

Wisnivesky et al. BMJ 2011, 343:d4013 and (J Clin Oncol 29: 2011 (suppl; abstr 7014)

Adjuvant Chemotherapy in Elderly

- Adjuvant chemotherapy is associated with survival benefit in the elderly and therefore it should not be denied to these patients.

- The benefit of adjuvant chemotherapy has not been established in patients 80 years of age or older and should be undertaken with extra caution.

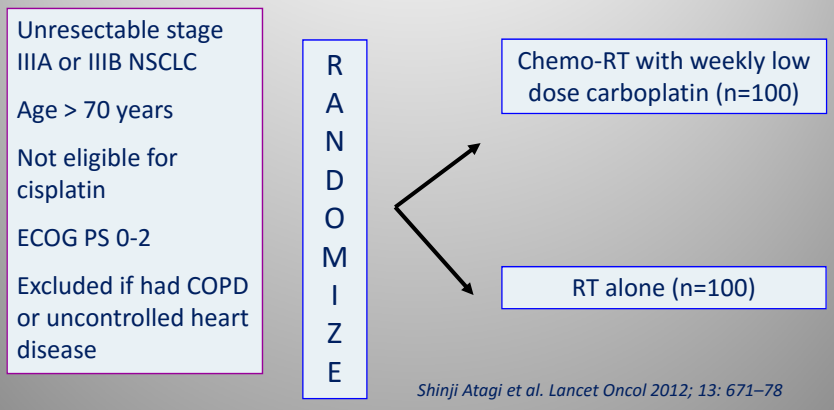
- Although there is lack of prospective data, carboplatin based regimen may be acceptable when patient is not a cisplatin candidate.

Locally Advanced NSCLC

- Elderly patients with locally advanced NSCLC are more likely to receive no treatment.
  - In one large series by Davidoff et al. based on SEER registry (n = 6325 patients, ≥66 years), 34% of these patients received no treatment at all.
  - Similarly Veterans Affairs Central Cancer Registry (n = 4635 patients, ≥65 years) reported that 35% of patients received no treatment.

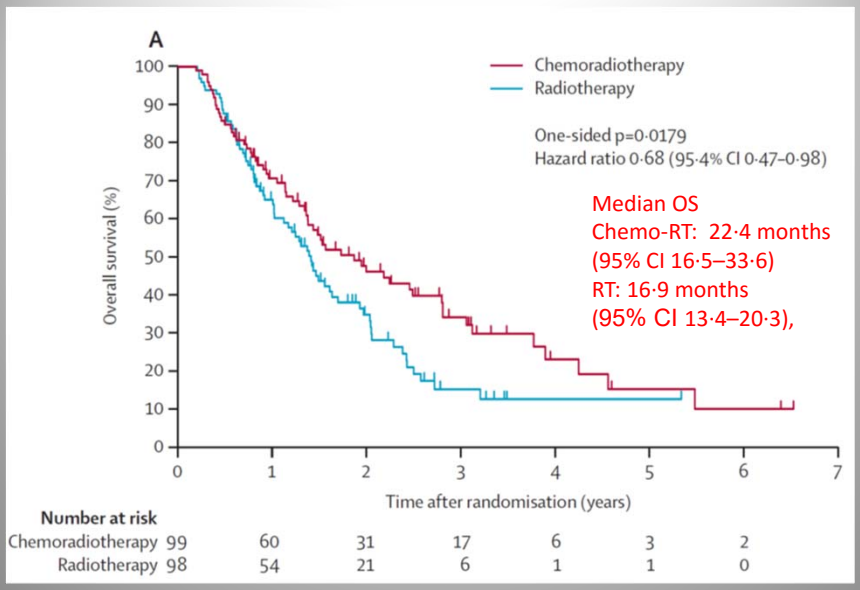
- Mixed data from the retrospective analyses of large randomized trials. Most post 2000 trials showed similar benefit of CRT (concurrent or sequential) compared to younger patients with increased toxicity. (NCCTG 94-24-52, CALGB and RTOG 94-10)

JCOG0301: A randomized, phase III trial of thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with NSCLC.



Shinji Atagi et al. Lancet Oncol 2012; 13: 671–78

Carboplatin was administered (30 mg/m2) 1 h before radiotherapy for the first 20 fractions, RT consisted of 60 Gy given as 30 fractions over 6 weeks.



Shinji Atagi et al. Lancet Oncol 2012; 13: 671–78.

Adverse Events

- Higher grade 3–4 hematological toxicity in Chemo-RT group than in the radiotherapy alone group. Neutropenia (57.3% *vs* none), and thrombocytopenia (29.2% *vs* 2.0%).
- Higher Grade 3 infection in Chemo-RT group (12.5%) than with radiotherapy (4.1%).
- Similar incidences of grade 3–4 pneumonitis and late lung toxicities between groups.

Shinji Atagi et al. Lancet Oncol 2012; 13: 671–78

- Only prospective randomized study showing benefit of CRT over RT alone in elderly.

- Several Limitations…
  - RT alone is not considered standard treatment for fit elderly patients
  - Weekly carboplatin/RT is not standard for concurrent chemo-RT for locally advanced disease.
  - Study only included Asian, good performance status (96.4% pts had PS 0 and 1)
  - Patients had limited co-morbidities (pts with COPD and uncontrolled heart disease were excluded).
  - Study did not include geriatric functional assessment of patients.

- Extrapolation of its conclusions to the general elderly western population should be made with caution.

Early Stage Disease

- Limited resections and omission of systematic mediastinal lymphadenectomy can be considered in the elderly on the basis of retrospective data.

- Pneumonectomy should be avoided when possible given the higher mortality associated with this procedure.

- VATS might be an option for elderly since it is associated with lower incidence of postoperative morbidity.

- For elderly patients who are not operable for medical reasons, SABR (stereotactic radiation) could represent an alternative with less adverse events and similar outcome, although prospective data are needed.

A. G. Pallis et al. Annals of Oncology 25: 1270–1283, 2014

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