Advances Standard of Care in Lung Cancer: A Best of ASCO Atlanta 2012 Update

EMORY
WINSHIP CANCER INSTITUTE
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Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small cell lung cancer?

～A pooled analysis of the literature～

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Background

- Approximately 30% of patients with NSCLC present with stage III locally advanced disease (LA-NSCLC).
- Patients with LA-NSCLC who have a good Performance Status (PS) and adequate organ function have a chance of long-term survival and could be potentially cured.
- Consolidation chemotherapy is an attractive approach, but, until now, few randomized studies have been reported.
- The Hoosier Oncology Group performed a randomized phase III study and reported that consolidation chemotherapy with docetaxel increased toxicities with no survival benefit.[1)]
- There is insufficient evidence indicating that consolidation chemotherapy improves survival without increasing toxicities.

1) Hanna N et al; J Clin Oncol 26: 5755-5760, 2008.

Objective

The purpose of this study is to determine whether consolidation chemotherapy is beneficial for patients with LA-NSCLC in terms of survival prolongation and toxicities.

Literature search

- We systematically searched PubMed for phase II or phase III trials published between January 1, 1995 and October 31, 2011, examining survival of concurrent chemo-radiotherapy for LA-NSCLC.
- The key words for systematic search were: ‘non-small cell lung cancer,’ ‘radiation or radiotherapy,’ ‘concurrent or concomitant’ and ‘phase II or phase III.’
- All search was limited to English language and studies with more than 30 patients per arm. Studies with no survival data were excluded.

Classification of studies examined

Without consolidation chemotherapy (CCT-)

Chemotherapy

Thoracic radiotherapy

PL: platinum
A, B: cytotoxic agent

With consolidation chemotherapy (CCT+)

Continuation consolidation chemotherapy (CCCT)

Switch consolidation chemotherapy (SCCT)

Results of systematic search

Systematic search using key words (n=1,209)

→ Not English-language (n=144), Not phase II or phase III (n=559)

Potentially relevant references identified and screened for retrieval (n=506)

→ Not clinical trials (n=98). Non NSCLC (n=40). Not concurrent chemoradiotherapy (n=26). Not phase II or phase III (n=102). Including Surgery or induction chemotherapy (n=105). No survival endpoint (n=15). Not platinum doublet chemotherapy (n=44). Small study size (n=14).

Potentially appropriate trials to be included (n=62)

→ OS did not reach to median (n=3). Including patients with Stage I/II/IV (n=5). Limiting to poor PS, poor risk, or elderly patients (n=8). Excluding patients with progressive diseases after chemoradiotherapy (n=3). Reanalyzed studies which are already included (n=2).

41 studies (7 PIII studies and 34 PII studies) with 45 arms.

Without CCT (CCT-): 20 arms
(No. of patients: 1,740)

With CCT (CCT+): 25 arms
(CCCT: 21 arms, SCCT: 4 arms)
(No. of patients: 1,707)

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Patient characteristics between two groups

	CCT-		CCT+		
	mean	SD	mean	SD	*p*
Age					0.222
median age	61.7	2.7	60.6	3.2	
Gender					0.633
% of female	22.0	12.5	23.8	12.9	
Histology					
% of Squamous cell carcinoma	47.6	9.9	43.7	12.2	0.261
% of Adenocarcinoma	35.6	8.9	36.0	12.5	0.904
Stage					0.665
% of Stage IIIA	35.7	19.2	33.2	18.4	
% of Stage IIIB	63.3	19.3	66.3	18.6	
Performance Status (PS)					0.652
% of PS 0	46.4	25.7	42.9	19.9	
% of PS 1	50.4	21.7	52.9	16.0	
% of PS 2	4.3	7.0	4.4	11.5	

There were no statistical differences between two groups.

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Treatment administrations

	CCT-		CCT+		
	mean	SD	mean	SD	*p*
Concurrent phase					
Planned TRT dose (Gy)	62.85	5.99	62.70	3.50	0.958
% of patients who completed TRT	85.65	10.89	89.18	7.66	0.285
% of patients who completed chemotherapies	86.15	13.03	79.16	14.47	0.142
Consolidation phase					
Number of planned CCT cycles	-	-	2.29	0.91	-
Median number of delivered CCT cycles	-	-	1.88	0.90	-
Mean number of delivered CCT cycles	-	-	1.53	0.64	-

The planned doses of thoracic radiotherapy were comparable between two groups. In concurrent phases, 80–90 % of patients had completed radiotherapy/chemotherapy in both groups.

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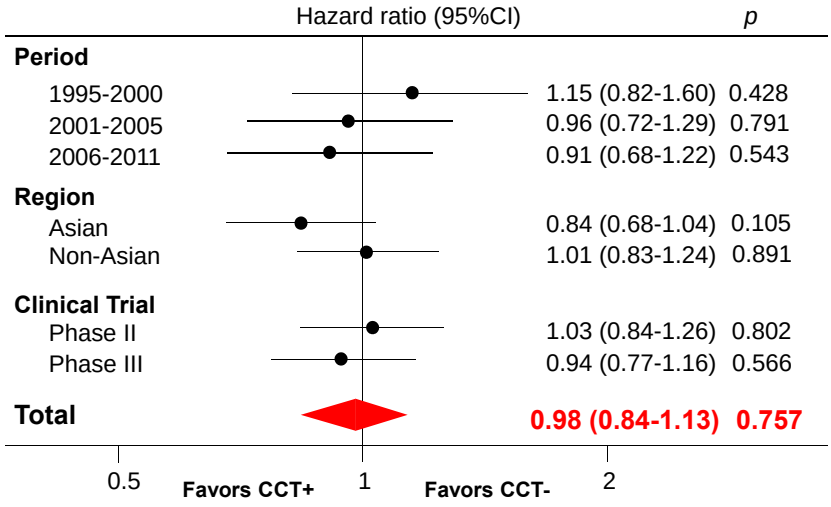
Subgroup analysis of hazard ratio (Comparison between CCT+ and CCT-)



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Toxicities between two groups

	CCT-		CCT+		
Grade 3-5 toxicities	mean	SD	mean	SD	*p*
Neutropenia (%)	50.50	28.41	45.36	24.41	0.634
Leukopenia (%)	58.10	33.12	54.70	22.40	0.743
Esophagitis (%)	14.79	14.68	15.97	12.17	0.776
Pneumonitis (%)	7.97	6.93	7.056	7.30	0.674
Treatment-related death (%)	2.30	2.04	1.96	2.68	0.628

Toxicities throughout the whole treatment courses were comparable.

Conclusions

- This pooled analysis on publication basis failed to provide evidence that consolidation chemotherapy improves overall survival in patients with LA-NSCLC.
- Clinical trials to evaluate the impact of consolidation chemotherapy are warranted.

Yamamoto et al-My non-ASCO sanctioned Conclusions and Questions

- Analysis of consolidation studies to date fails to provide a compelling rationale either for or against this approach.
- The trials evaluated had a mixture of stages, patient performance status and agents.
- Concurrent chemo-radiotherapy with cisplatin based chemotherapy is the standard approach, with the need to assess consolidation therapy in the context of targeted in terms of genomic driven therapies.
- Consolidation chemotherapy should be tested in a trial with robust accrual numbers, only in responding patients who have an excellent PS at the end of chemo-radiation therapy..

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Accuracy of FDG-PET to diagnose lung cancer in the ACOSOG Z4031 trial

E. L. Grogan, S.A. Deppen, K.V. Ballman, G. Andrade, F. Verdail, M.C. Aldrich, H. Chen, P. Decker, D. Harpole, R. Cerfolio, R. Keenan, D. R. Jones, T. A. D'Amico, J. Shrager, B. Meyers, J.B. Putnam

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Background

- NCCN guidelines recommend FDG-PET for diagnosis of suspected NSCLC
- FDG-PET highly accurate in meta-analysis
  - Sensitivity 94%
  - Specificity 83%[1]
- FDG-PET performed poorly [2,3]
  - Single institution case series
  - Endemic fungal lung disease

[1]Gould et.al. JAMA 2001
[2]Deppen et.al. Ann Thor Surg 2011
[3]Croft et.al. Lung Cancer 2002

Purpose

1) To evaluate the accuracy of FDG-PET to diagnose NSCLC in patients undergoing resection for c-Stage I disease in a national population
2) To examine differences in sensitivity and specificity between enrolling cities

Population- ACOSOG Z4031 study

- "Use of proteomic analysis of serum samples for detection of NSCLC"
- Known or suspected c-Stage I NSCLC
- All underwent surgical resection
  - 2004 to 2006
  - 51 sites in 39 cities
  - 969 eligible participants
  - 80% cancer / 20% benign

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Details for Z4031 study

- Inclusion / exclusion criteria
  - Clinically suspicious Stage 1 lung lesion
  - CT imaging < 60 days prior to lung resection
  - No prior malignancy < 5 years prior
- Data collected
  - Demographics
  - Imaging results / operative notes /pathology reports
  - Serum / tissue
  - Survival

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Methods for current study

- Secondary analysis of prospective trial
- Population
  - Z4031 eligible patients
  - **682 patients** with FDG-PET scans
- Outcome classification
  - Cancer
  - Pathology report
- FDG-PET categorization
  - Radiologists reports reviewed

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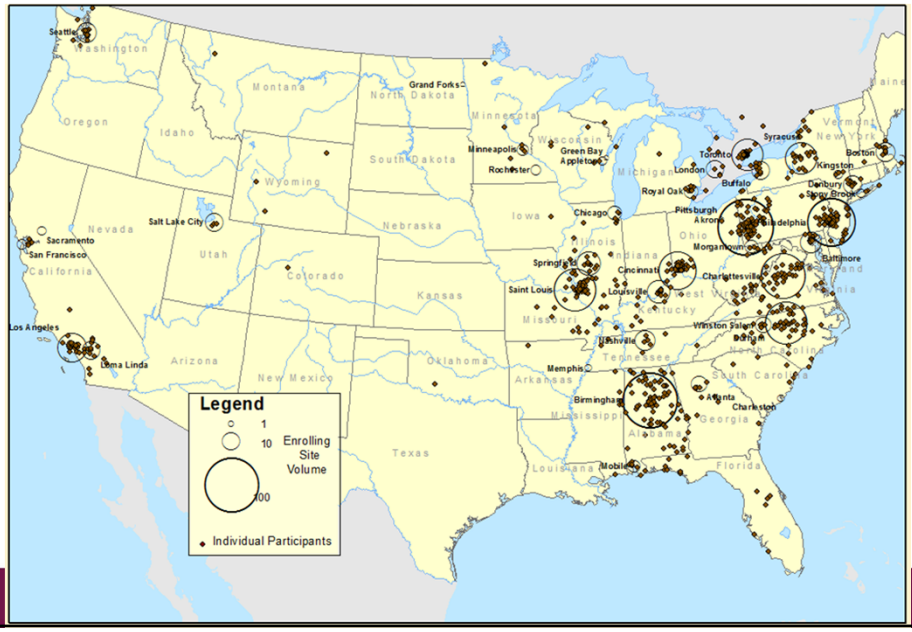
Results – Z4031 participants - PET



Results – FDG-PET

Malignancy	566 (83%)
Accuracy (TP+TN)/N	73%
Sensitivity	**82%**
Specificity	**31%**
Positive Predictive Value	85%
Negative Predictive Value	26%

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Results – FDG-PET (2x2)

		Diagnosis	
		Cancer	**Benign**
FDG-PET Result	**Avid**	**465** True Positive	**80** False Positive
	Non Avid	**101** False Negative	**36** True Negative

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FDG-PET results

- False positives (80)
  - 69% granulomas
- False negatives (101)
  - 11 patients ≤10 mm
    - 9 adeno, 1 squamous, 1 other
  - Pathology
    - 62% Adenocarcinoma
    - 11% Squamous
    - 10% BAC
    - 9% Neuroendocrine
    - 8% Other

FDG-PET Results by Enrolling Site*

City	N	Sensitivity	Specificity
Birmingham, AL	111	89	15
Charlottesville, VA	52	76	33
Cincinnati, OH	31	73	33
Durham, NC	41	91	25
Los Angeles, CA	27	67	44
Philadelphia, PA	78	85	46
Pittsburg, PA	68	78	25
St. Louis, MO	54	68	29
		p = 0.03	p = 0.72

* > 25 participants with a FDG-PET scan

Summary slide

- FDG-PET performed poorly for diagnosing NSCLC in a national sample of c-Stage I patients
  - Sensitivity - 82%
  - Specificity - 31%
- Majority of false positives were granulomas
- Sensitivity varies by enrolling city
- FDG-PET accuracy improved with lesion size
  - Accuracy < 50% for < 2cm lesions

Summary slide - Strengths

- National dataset
  - Largest series evaluating accuracy of FDG-PET in patients with known or suspected clinical stage 1 NSCLC
- Generalizable to clinical practice
  - Multiple FDG-PET scanners
  - Different radiology practices
  - Community and academic centers

Summary slide - Limitations

- Secondary analysis of a prospective study
- 67% SUV values available
  - Some centers do not report
- PET was performed for diagnosis and staging
- Did not have original images
  - Relied on written reports

Conclusions

- FDG-PET did not perform as well as previously published in c-stage 1 patients with NSCLC undergoing surgical resection
  - Should be used cautiously
  - Reasons should be explored
- Sensitivity varied across enrolling sites
  - Geographic variation

Grogan et al-My non-ASCO sanctioned Conclusions and Questions

- Quality of and experience with PET scans vary widely across the US.
- The degree of false negatives and therefore the negative predictive value of PET in stage I NSCLC is disturbing.
- This study further enforces the need for mediastinoscopy in resectable stage lung cancer.
- The interpretations are substantially limited by the fact that this is a secondary analysis without access to the actual PET images.

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Phase III Trial of Concurrent Thoracic Radiotherapy (TRT) with Either the 1st Cycle or the 3rd Cycle of Cisplatin and Etoposide Chemotherapy to Determine the Optimal Timing of TRT for Limited-Disease Small Cell Lung Cancer (NCT01125995)

Keunchil Park,[1] **Jong-Mu Sun**,[1] **Sang-We Kim**,[2] **Yong Chan Ahn**,[1] **Eun Kyung Choi**,[2] **Myung-Ju Ahn**,[1] **Jin Seok Ahn**,[1] **Se-Hoon Lee**,[1] **Sin-Ho Jung**,[3] **Dae Ho Lee**,[2] **Hongryull Pyo**,[1] **Si Yeol Song**,[2] **Jungmin Jo**,[2] **Hee Jung Sohn** [2] **Cheolwon Suh**,[2] **Jung Shin Lee**[2]

[1]Samsung Medical Center, Seoul, Republic of Korea; [2]Asan Medical Center, Seoul, Republic of Korea; [3]Duke University, Durham, NC, USA

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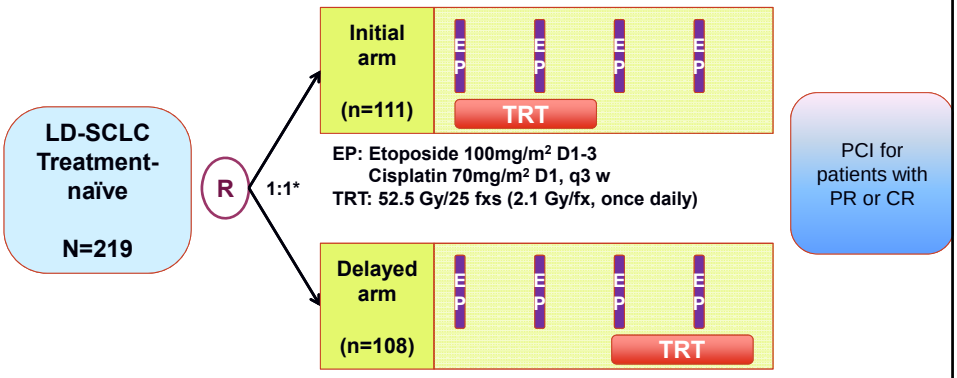
Background

- The standard treatment of LD-SCLC is concurrent thoracic radiotherapy (TRT) with chemotherapy
- However, the optimal timing of TRT has not yet been defined
- Limitations in early initiation of TRT given with the 1st cycle of chemotherapy
  - Potentially enlarged radiation fields due to initial planning for bulky tumors
  - Complexity of administering TRT results in delayed overall treatment for LD-SCLC
- This study aimed to investigate whether TRT commenced with the 3rd cycle of EP chemotherapy is non-inferior to TRT commenced with the 1st cycle of EP chemotherapy

Study Design



- Primary end point: Complete response rate (WHO criteria)
- Secondary end point: ORR, OS, PFS, and toxicity (NCI-CTC ver. 2.0)

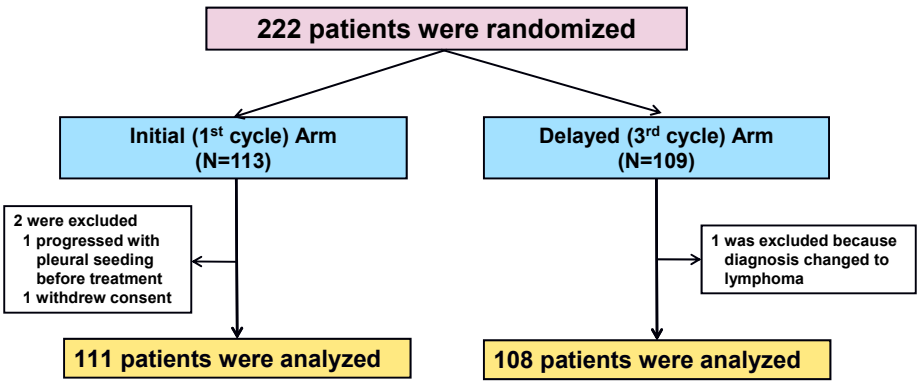
*Stratified by the institute
Response evaluation: every 2 cycles during treatment, every 3 mo. for 1 Y, and then every 6 mo.

Key Inclusion Criteria

- Histologically confirmed SCLC
- Limited disease
- Measurable lesion(s)
- Age ≥ 18 years
- Performance status, ECOG 0-2
- Adequate hematologic, hepatic, and renal function
- No prior history of chemotherapy, radiotherapy, or surgery for SCLC
- Written informed consent

Consort Diagram

- Enrollment between July 2003 and June 2010
- Median follow-up: 59.4 months (range: 14.9 – 97.5 months)



*Cut-off date for survival analysis: August 20 2011

Patient Demographics

	Total n=219, (%)	Initial Arm n=111, (%)	Delayed Arm n=108, (%)	P
Age (years)				
Median (range)	61 (39-75)	60 (41-75)	61 (39-75)	
> 60 years	111 (50.7)	53 (47.7)	58 (53.7)	0.4
≤ 60 years	108 (49.3)	58 (52.3)	50 (46.3)	
Sex				0.9
Male	194 (88.6)	98 (88.3)	96 (88.9)	
Female	25 (11.4)	13 (11.7)	12 (11.1)	
Performance status				0.14
ECOG 0	17 (7.8)	12 (10.8)	5 (4.6)	
ECOG 1	201 (91.8)	99 (89.2)	102 (94.4)	
ECOG 2	1 (0.5)	0	1 (0.9)	
Institute				0.8
Samsung Medical Center	112 (51.1)	56 (50.5)	56 (51.9%)	
Asan Medical Center	107 (48.9)	55 (49.5)	52 (48.1%)	

Treatment Exposure

	Initial arm n=111, (%)	Delayed arm n=108, (%)	P
Completion of EP x 4 & RT 52.5Gy			0.80
Yes	90 (81.1)	89 (82.4)	
No	21 (18.9)	19 (17.6)	
No. of EP chemotherapy			0.49
4 cycles	96 (86.5)	97 (89.8)	
3 cycles	6 (5.4)	3 (2.8)	
2 cycles	7 (6.3)	4 (3.7)	
1 cycle	2 (1.8)	4 (3.7)	
Dose of chemotherapy			0.95
Relative dose intensity	93.5%	93.6%	
Dose of radiotherapy			0.77
52.5Gy	100 (90.1)	96 (88.9)	
< 52.5Gy	11 (9.9)	12 (11.1)	
Mean dose	51.0 Gy	49.5 Gy	0.24
Delivery of radiotherapy			0.91
Uninterrupted RT	100 (90.1)	97 (89.8)	
Major interruption of RT (<47.25Gy, <90%)	6 (5.4)	7 (6.5)	
Minor interruption of RT (≥47.25Gy, ≥90%)	5 (4.5)	4 (3.7)	
Prophylactic cranial irradiation			0.37
Yes	55 (49.5)	60 (55.6)	
No	56 (50.5)	48 (44.4)	

Objective Response

	Initial Arm (n = 111)	Delayed Arm (n = 108)	95% CI of the difference
CR	40 (36.0%)	41 (38.0%)	(-14.7%, 10.9%)
PR	62 (55.9%)	56 (51.9%)	
SD	4 (3.6%)	4 (3.7%)	
PD	5 (4.5%)	5 (4.6%)	
Unknown	0	2 (1.9%)	
ORR (CR+PR)	91.9%	89.8%	

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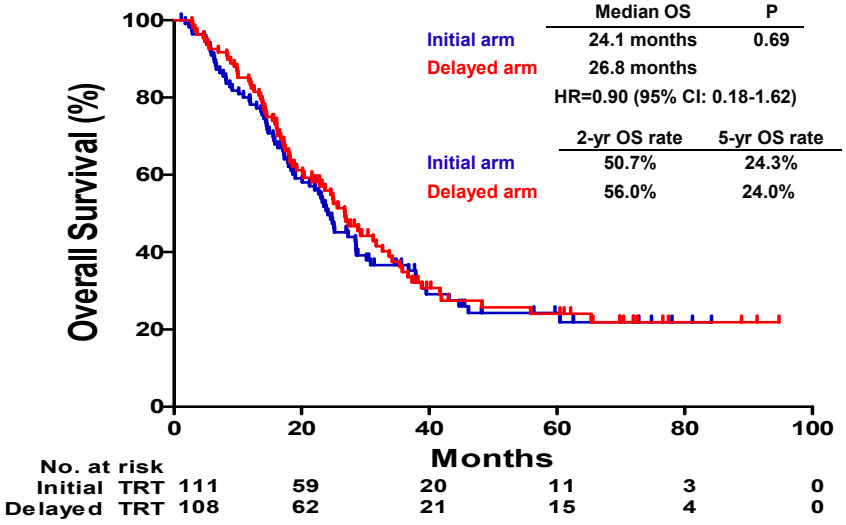
Overall Survival



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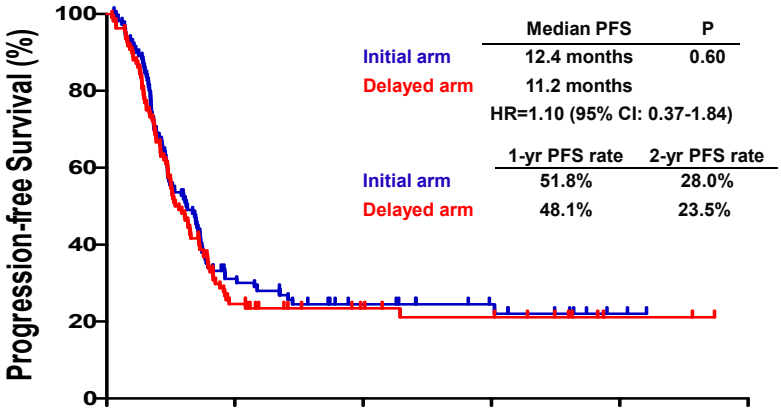
Progression-free Survival



	Median PFS	P
Initial arm	12.4 months	0.60
Delayed arm	11.2 months	

HR=1.10 (95% CI: 0.37-1.84)

	1-yr PFS rate	2-yr PFS rate
Initial arm	51.8%	28.0%
Delayed arm	48.1%	23.5%

No. at risk						
Initial TRT	111	30	17	11	3	0
Delayed TRT	108	24	13	10	3	0

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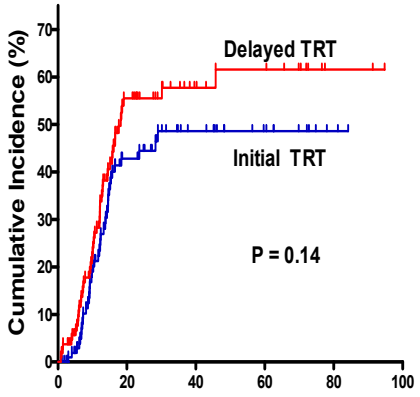
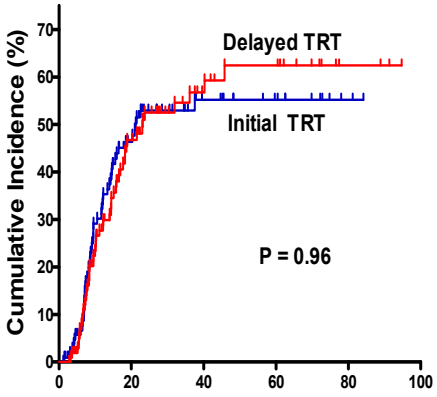
Pattern of Failure

Locoregional Failure



No. at risk						
Initial TRT	111	41	19	11	3	0
Delayed TRT	108	32	14	11	3	0

Distant Failure



No. at risk						
Initial TRT	111	42	18	11	3	0
Delayed TRT	108	43	18	13	4	0

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Toxicity

	Grade 3-4		All adverse events		
	Initial (n =111)	Delayed (n = 108)	Initial (n =111)	Delayed (n = 108)	P
Non-hematologic					
Nausea	1.9%	0.9%	56.8%	58.3%	0.81
Vomiting	0	0	13.5%	14.8%	0.78
Esophagitis	3.6%	0.9%	45.0%	37.0%	0.23
Constipation	0	0	19.8%	25.9%	0.28
Diarrhea	0	0	2.7%	4.6%	0.45
Sensory neuropathy	0	0	10.8%	18.5%	0.11
Radiation pneumonitis	4.5%	2.8%	80.2%	75.9%	0.53
Hemorrhage	0.9%	0	0.9%	0.9%	0.98
Infection without neutropenia	1.9%	1.9%	4.5%	6.5%	0.52
Hematologic					
Febrile neutropenia*	21.6%	10.2%	21.6%	10.2%	0.02
Neutropenia	70.3%	59.3%	77.5%	67.6%	0.10
Anemia	9.9%	6.5%	30.6%	33.3%	0.67

*Three and two patients died in the initial and the delayed arms, respectively

Post-progression Chemotherapy

	Initial arm	Delayed arm
No. of patients with Progression	66 (100%)	71 (100%)
Salvage chemotherapy		
1 line	52 (79%)	48 (68%)
2 lines	20 (30%)	21 (30%)
≥ 3 lines	7 (11%)	13 (18%)

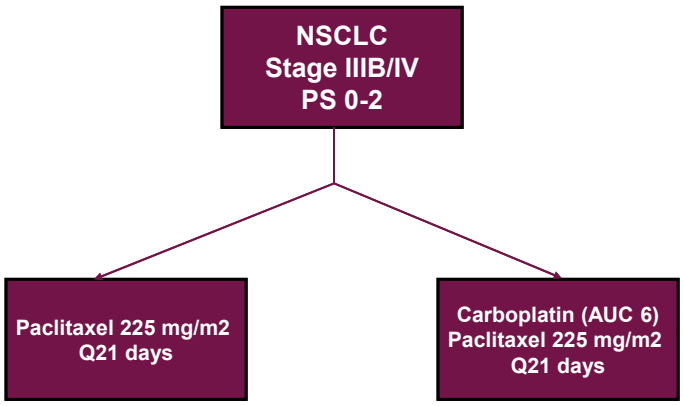
Summary

- **Concurrent TRT with the 3rd cycle of EP chemotherapy was non-inferior to the 1st cycle of EP chemotherapy in terms of CR rate**
- **The OS and PFS outcomes in the delayed TRT arm were comparable to those of the initial TRT arm**
- **TRT with the 3rd cycle of EP is associated with lower incidence of neutropenic fever than TRT with the 1st cycle of EP**

A Phase III Randomized Trial of Single Agent Pemetrexed vs. Carboplatin and Pemetrexed in Patients with Advanced Non-Small Cell Lung Cancer and a Performance Status of 2

ogerio Lilenbaum, Mauro Zukin, Jose Rodrigues Pereira, arlos H. Barrios, Ronaldo De Albuquerque Ribeiro, Carlos A gusto de Mendonça Beato, Yeni Neron do Nascimento, dre Murad, Fabio A. Franke, Maristela Precivale, Luiz nrique de Lima Araujo, Clarissa Serodio Da Rocha ldotto, Fernando Meton Vieira, Isabele Avila Small, rlos G. M. Ferreira

CALGB 9730



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CALGB 9730: PS 2 Subset Analysis

	Total		PS 2		
	P	CP	P	CP	All
N	277	284	50	49	99
OR (%)	17	30	10	24	17
MST (mo)	6.7	8.8	2.4	4.7	3.1
1-yr OS%	32	37	10	18†	14
2-yr OS%	NA	NA	0	9	5

†Log rank p = .0123

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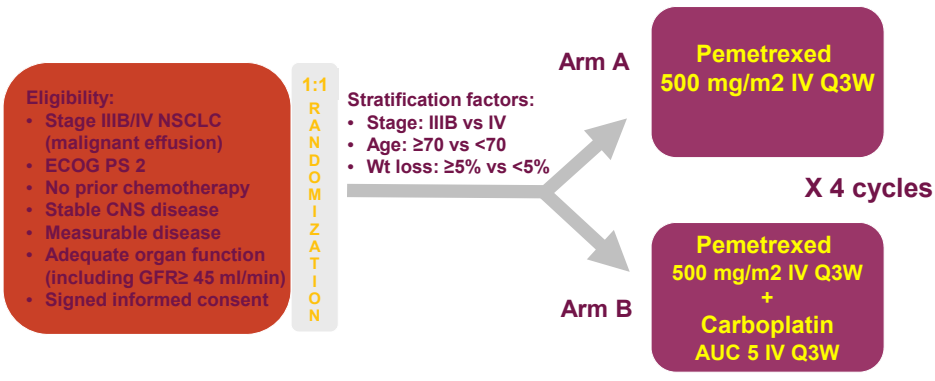
Main Objectives

- A dedicated prospective phase III comparison of single agent versus combination chemotherapy in PS 2 patients
- To develop a research infrastructure in Brazil to conduct investigator-initiated multi-center clinical trials

Trial Design

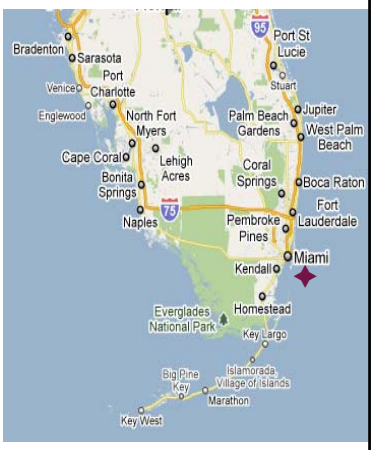


Primary endpoint:
Overall Survival

Secondary endpoints:
Progression-free survival
Overall response rate
Safety

Pre-medications:
Vitamin B12: 1mg IM Injection
Folic Acid: 350-1,000mcg po daily
Dexamethasone 4mg po BID the day before, the day of, and the day after

Logistics



Brazil: 8 centers
US: 1 center

Coordinating Center:

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Patient Characteristics

	P (n=102)	CP (n=103)	
Median age (range)	65 (40-86)	65 (41-90)	
≥70 y (%)	(35.2)	(36.8)	
Male / Female (%)	58.8 / 41.2	63.1 / 36.9	
Stage IIIB / IV (%)	4.9 / 95.1	5.8 / 94.2	
≥5% Weight loss (%)	53.9	51.4	
Histology (%)			
Adenocarcinoma	80.4	81.6	
Squamous cell	10.8	2.9	p=0.123
Unknown	4.9	5.8	
Smoking Status (%)			
Current	10.8	17.5	
Former	66.7	60.2	
Never	22.5	22.3	
Co-Morbidities (%)			
Hypertension	45.1	44.7	

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Treatment Delivery

	P	CP
Median	**4**	**4**
Treatment completed	39%	61%*
• Carboplatin (AUC) - median	5	5
• Pemetrexed – median	500	500
Treatment discontinuation	47 (61%)	30 (39%)
• early death	15	10
• early progression	15	9
• clinical deterioration	13	7
• toxicity	0	2
• other	4	2
	43	26
Therapy delay	**20.6%**	**44.7%**
Dose reductions	**2%**	**3.9%**

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Response Data

	P (%)	CP (%)
CR	0	2.5
PR	10.5	21.5
SD	42.6	60.8
PD	47.1	15.2
ORR (CR+PR)	10.5	24.0*

*** P < 0.029**

33.3% of patients in P and 23.3% in CP were

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Toxicity

G3/4 Toxicity (%)	P		CP
Anemia	3.9	p=0.066	11.7
Thrombocytopenia	0		1.0
Neutropenia	1.0	p=0.119	5.8
Febrile Neutropenia	2.9	p=0.683	1.9
Nausea/Emesis	0		2.9
Diarhea	2		1
Dyspnea	10.8		5.8
Grade 5 Events	0	p=0.121	3.9*

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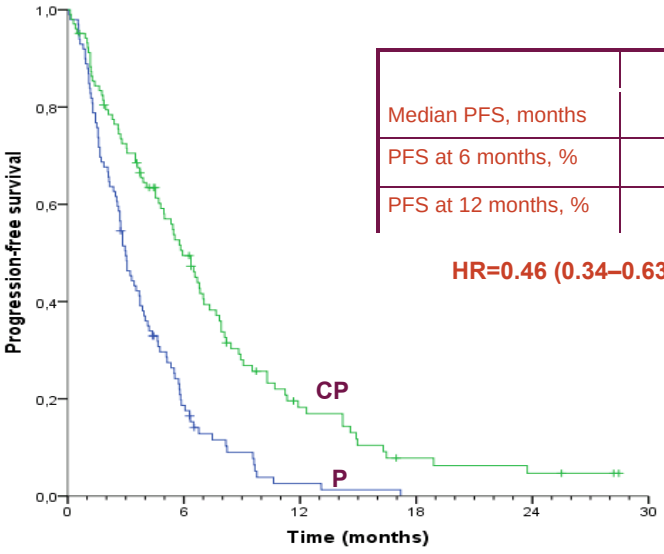
PROGRESSION-FREE SURVIVAL



	P	CP
Median PFS, months	3.0	5.9
PFS at 6 months, %	17	47
PFS at 12 months, %	4	18

HR=0.46 (0.34–0.63); p<0.001

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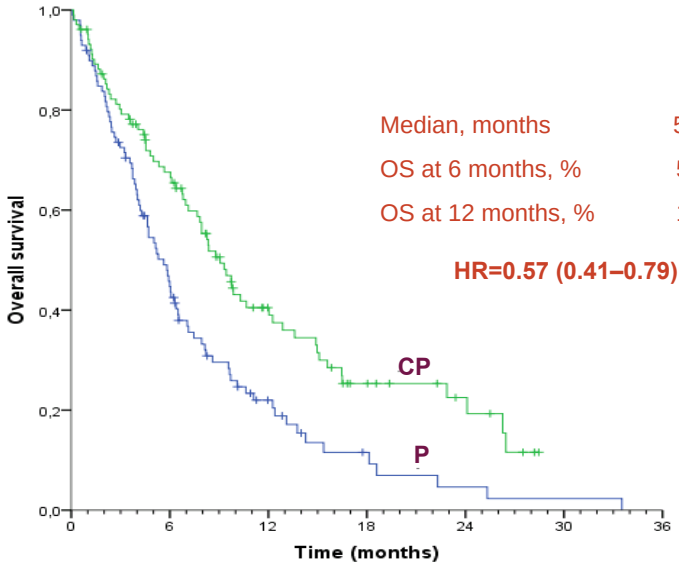
OVERALL SURVIVAL



	P	CP
Median, months	5.6	9.1
OS at 6 months, %	50	65
OS at 12 months, %	18	43

HR=0.57 (0.41–0.79); p=0.001

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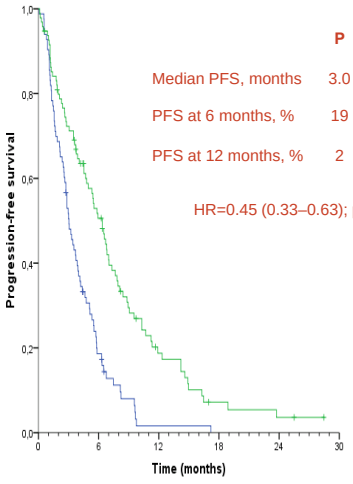
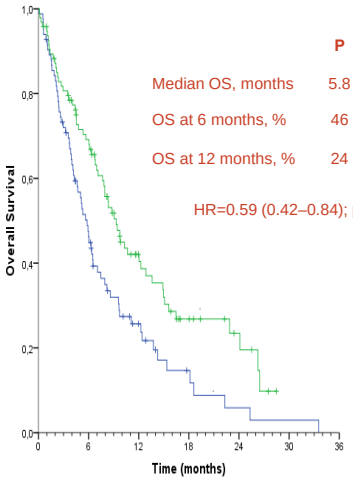
Survival without Squamous/Unknown



	P	CP
Median PFS, months	3.0	6.3
PFS at 6 months, %	19	51
PFS at 12 months, %	2	19

HR=0.45 (0.33–0.63); p<0.001

Progression-Free Survival



	P	CP
Median OS, months	5.8	9.3
OS at 6 months, %	46	68
OS at 12 months, %	24	40

HR=0.59 (0.42–0.84); p=0.003

Overall Survival

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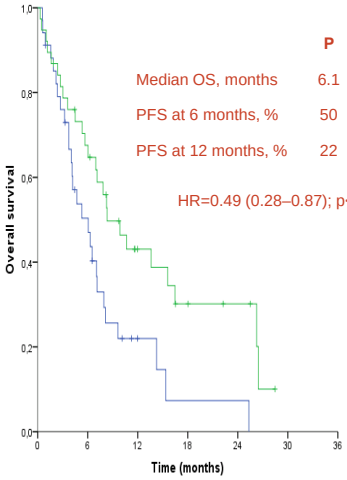
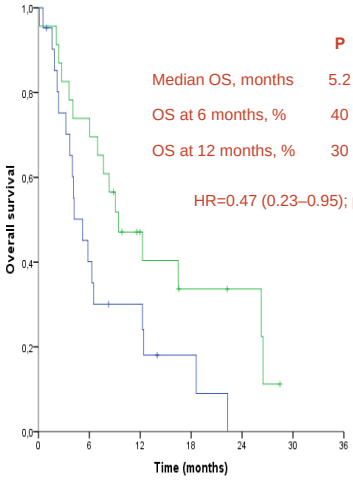
Elderly and Never Smokers



	P	CP
Median OS, months	6.1	8.3
PFS at 6 months, %	50	65
PFS at 12 months, %	22	43

HR=0.49 (0.28–0.87); p<0.015



	P	CP
Median OS, months	5.2	9.4
OS at 6 months, %	40	70
OS at 12 months, %	30	47

HR=0.47 (0.23–0.95); p<0.035

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Second-Line Therapy

Therapy	P (%)	CP (%)
Any	31	29.5
Chemotherapy		
Pemetrexed	3	12
Docetaxel	19	30
Paclitaxel	15	12
Carboplatin	31	15
EGFR TKI	9	12
Other	17	16
Unknown	6	3

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Conclusions

- Combination chemotherapy with carboplatin-pemetrexed significantly improves survival compared to single agent pemetrexed in patients with advanced NSCLC and a PS of 2
- The secondary endpoints of response rate and progression-free survival were also met
- The survival benefit was maintained in subset populations
- Toxicity was acceptable in this high-risk group

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Implications for Practice

- These results can be generalized to PS 2 patients with all histological subtypes, using appropriate combination regimens
- Given the magnitude of the benefit, and the immediate applicability of these data to clinical practice, we urge organizations to revise their guidelines
- The research mechanism developed for this trial serves as a model for future investigator-initiated multi-center trials in Brazil and other Latin American countries

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Lillenbaum et al-My non-ASCO sanctioned Conclusions and Questions

- In selected PS 2 patients, combination chemotherapy appears superior to single agent chemotherapy.
- How broadly these results can be generalized to PS 2 patients with all histological subtypes, is open to question, as methods of documenting performance status in this trial were not clear.
- It may be reasonable to use appropriate combination regimens in selected Ps1/2 patients with close observation in clinical practice until a confirmatory trial is completed.
- Despite the magnitude of the possible benefit, and the immediate applicability of these data to clinical practice, it may be premature to revise treatment guidelines for PS 2 patients with metastatic NSCLC.

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