Early Stage Lung Cancer – Adjuvant Chemotherapy

Dr Suhas Aagre

Consultant Medical Oncologist & Hemato-Oncologist,
Asian Cancer Institute, Mumbai.

Asian Cancer Institute
Reviving Hopes...

Adjuvant Chemotherapy – Why ?

Surgical stage	5-yr survival%	relapse % local	distant
IA T1N0M0	67	10	15
IB T2N0M0	57	10	30
IIA T1N1M0	55		
IIB T2N1M0 T3N0M0	39 38	12	40
IIIA T3N1M0 T1-3N2M0	25 23	15	60

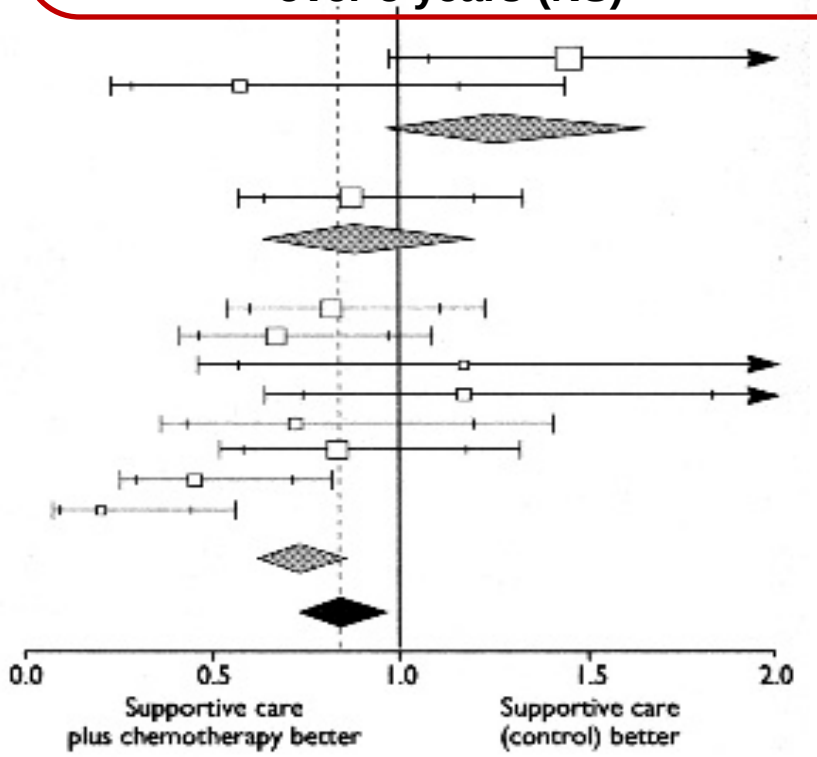
1. Mountain 2. Feld 84 3. Pairolera 84 4. Martini 80 5. Thomas 90 6. Scagliotti ASCO 2004

BMJ Meta-analysis 1995

Alkylators:15 % increased risk of death

Cisplatin Based : 13 % reduction in risk of death ,absolute benefit 5% over 5 years (NS)

Trial	No of events/ No of patients entered: Supportive care plus chemotherapy	Supportive care	Observed − expected deaths	Variance
Long term alkylating agents:				
Oxford	120/121	62/67	16.40	43.80
Quebec	20/20	18/18	-4.38	7.99
Subtotal	140/141	80/85	12.02	51.79
Vinca alkaloids/etoposide:				
Gwent 2	96/111	67/75	-5.15	38.00
Subtotal	96/111	67/75	-5.15	38.00
Cisplatin based:				
RLW 8351	84/86	80/81	-8.06	39.94
NCIC CTG	95/97	51/53	-11.28	28.24
Southampton	17/17	15/15	1.16	7.55
NRH	44/44	40/43	2.93	18.72
UCLA	31/32	30/31	-4.83	14.53
Ancona 1	63/63	65/65	-5.72	30.95
AOI-Udine	52/52	50/50	-14.98	18.77
CEP-85	23/25	21/24	-10.52	6.61
Subtotal	409/416	352/362	-51.31	165.31
Total	645/668	499/522	-44.44	255.09



BMJ 1995;311:899

Asian Cancer Institute
Reviving Hopes...

Why Failure

1. Small sample size
2. Several methodological flaws
3. Poor compliance to chemotherapy
4. Significant surgical procedure like thoracotomy
5. Suboptimal supportive measures like antiemetic and G-CSF support

Artal Cortés Á, Calera Urquizu L, Hernando Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. Transl Lung Cancer Res. 2015 Apr;4(2):191-7. doi: 10.3978/j.issn.2218-6751.2014.06.01. PMID: 25870801; PMCID: PMC4384209.

The NEW ENGLAND JOURNAL of MEDICINE

Asian Cancer Institute

ORIGINAL ARTICLE

Cisplatin-Based Adjuvant Chemotherapy in Patients with Completely Resected Non–Small-Cell Lung Cancer

The International Adjuvant Lung Cancer Trial Collaborative Group*

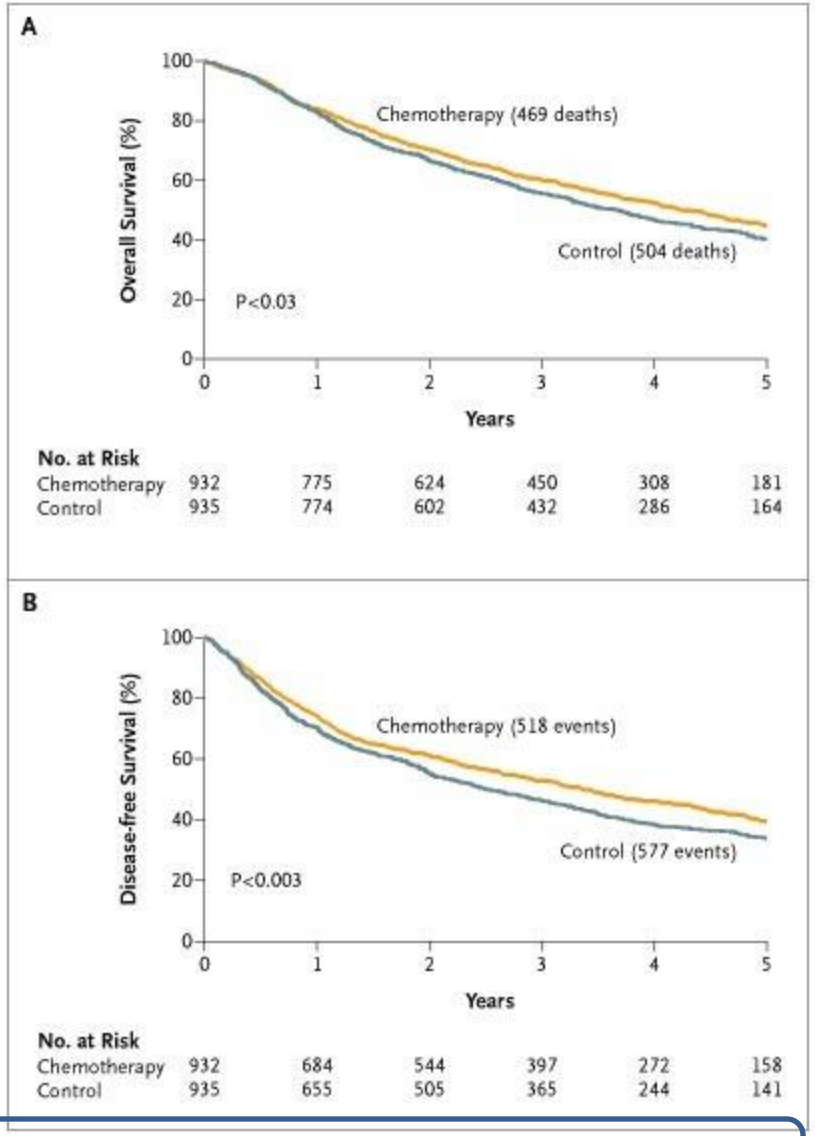
Largest sample size (1867 patients)

1st study showing Significant higher survival [44.5% vs. 40.4% at 5 years; HR 0.86 (95% CI, 0.76-0.98, P<0.03)].

Superior PFS [39.4 vs. 34.3 at 5 years [HR 0.83 (95% CI, 0.74-0.94, P <0.003)]

0.8% of chemotherapy-related deaths

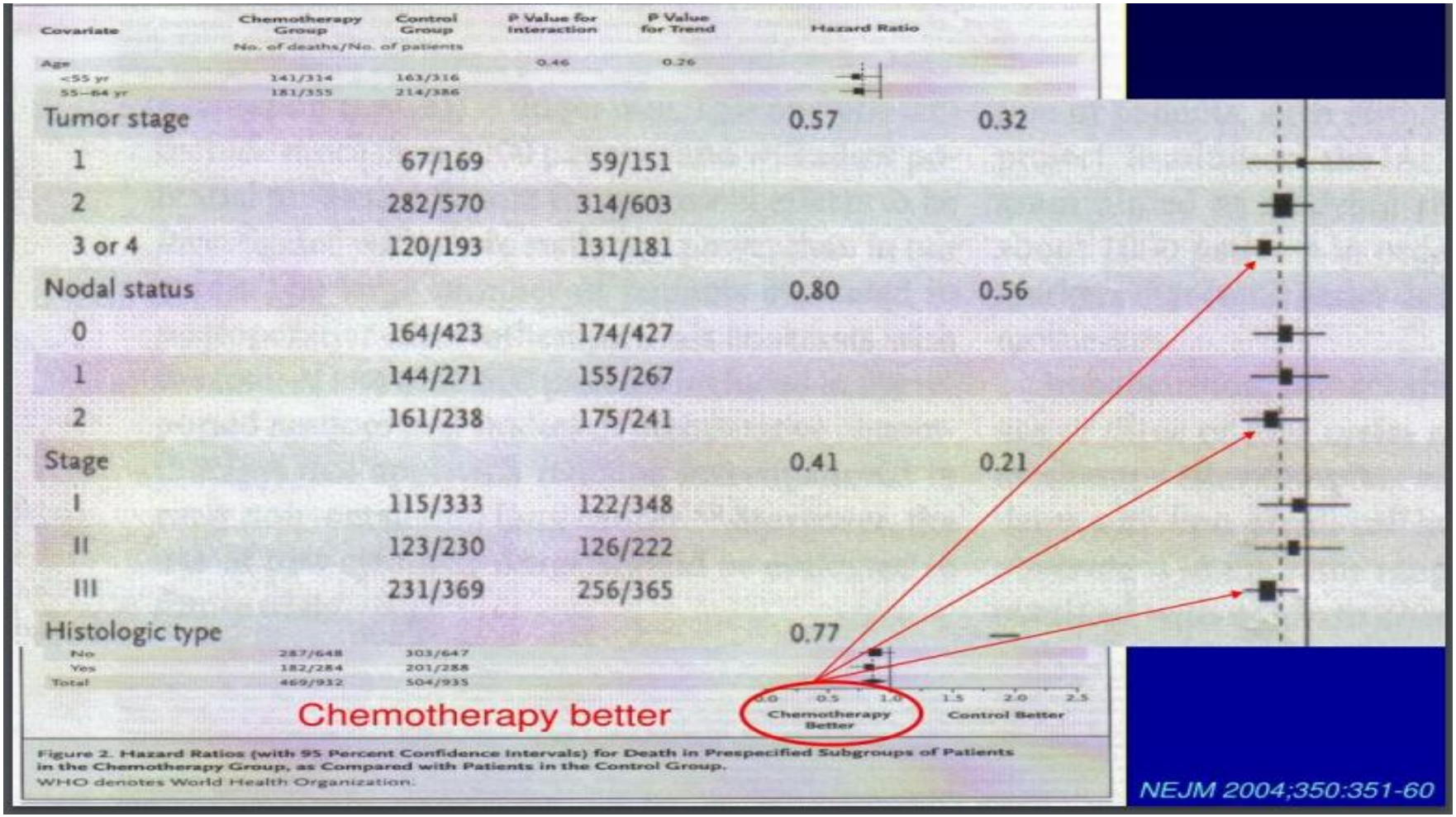
Led to the clinical implementation of adjuvant chemotherapy



Arriagada R, Bergman B, Dunant A, et al. Cisplatinbased adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351-60.

Asian Cancer Institute
Reviving Hopes...

IALT



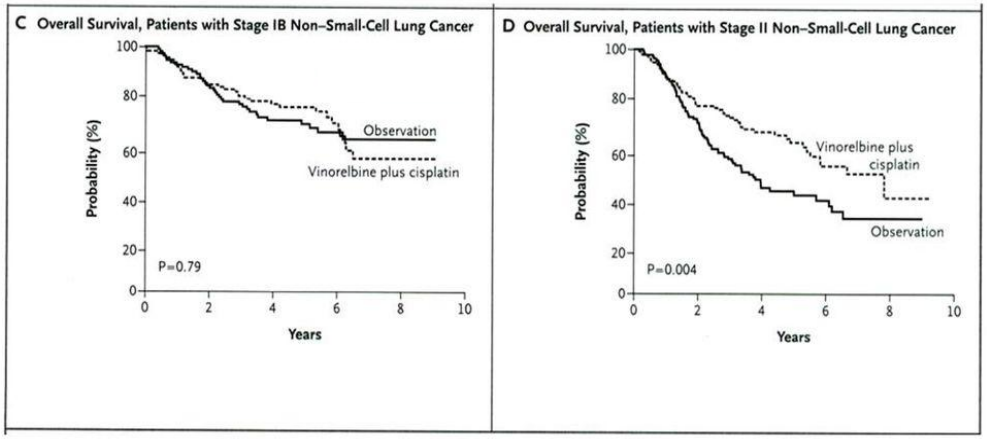
NCIC CTG JBR. 10 trial

Asian Cancer Institute
Reviving Hopes...

- **The effect of adjuvant vinorelbine plus cisplatin on survival ?**
  - ***4 cycles of vinorelbine plus cisplatin* vs. observation**
  - **482 pts: 242 pts (CTx) vs. 240 pts (Obs)**
    - **Stage IB, stage II (except, T3N0)**
    - **1994/4 - 2001/4**
    - **CALGB, SWOG, ECOG joined in 1998**
    - **Canadian and American**

NEJM 2005;352:2589-97

NCIC CTG JBR. 10 trial



No survival benefit for stage IB patients (P=0.79)

Stage II median survival : 80 months for the chemotherapy arm vs. 41 months for the observation arm [HR 0.59 (95% CI, 0.42-0.85, P=0.004)]

NEJM 2005;352:2589-97

FAST TRACK — ARTICLES | VOLUME 7, ISSUE 9, P719-727, SEPTEMBER 01, 2006

Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial

Dr, Prof Jean-Yves Douillard, MD • Prof Rafael Rosell, MD • Mario De Lena, MD • Francesco Carpagnano, MD • Rodryg Ramlau, MD • Jose Luis Gonzáles-Larriba, MD • et al. Show all authors

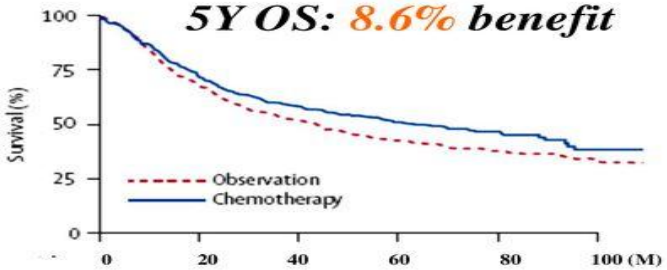
Published: August 16, 2006 • DOI: https://doi.org/10.1016/S1470-2045(06)70804-X

Asian Cancer Institute
Reviving Hopes...

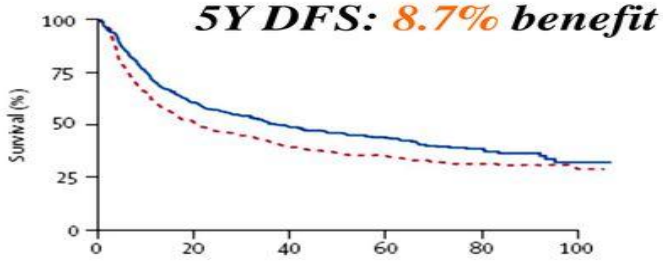
ANITA Trial

Median F/U: 76 months

5Y OS: 8.6% benefit



5Y DFS: 8.7% benefit



Overall survival

HR 0.80

(p=0.017)

Survival Benefit (+)

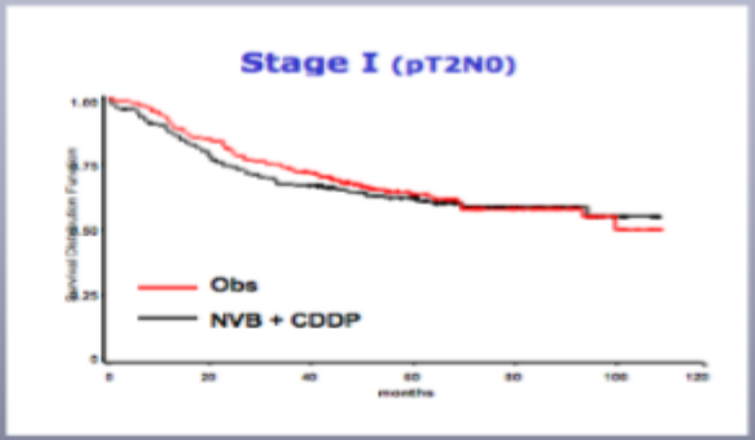
Disease free survival

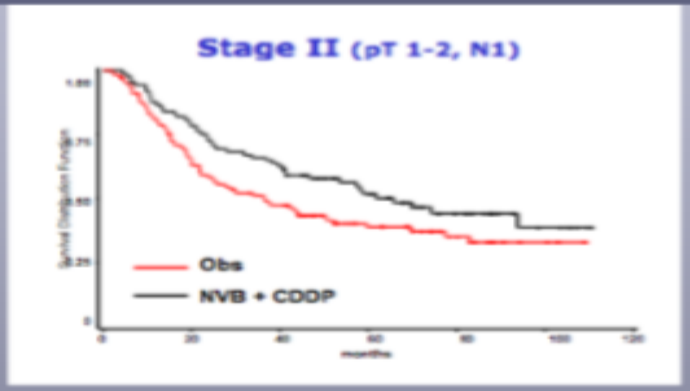
HR 0.76

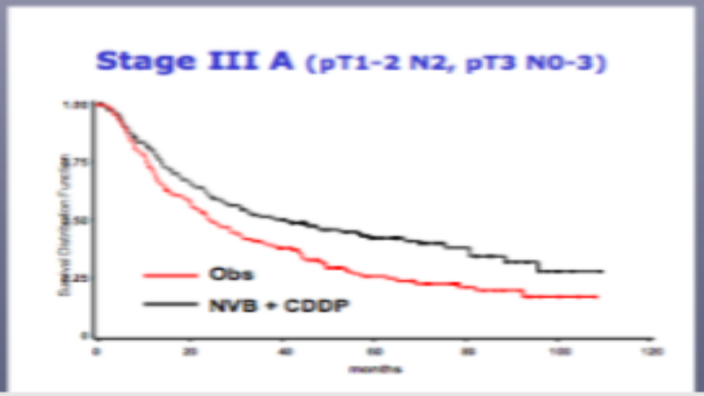
(p=0.002)

Lancet Oncol 2006;7:719-27

Adjuvant chemotherapy, survival by stage - ANITA







ANITA
Clear benefit in stage II and IIIa

Adjuvant Paclitaxel Plus Carboplatin Compared With Observation in Stage IB Non–Small-Cell Lung Cancer: CALGB 9633 With the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups

Gary M. Strauss, James E. Herndon II, Michael A. Maddaus, David W. Johnstone, Elizabeth A. Johnson, David H. Harpole, Heidi H. Gillenwater, Dorothy M. Watson, David J. Sugarbaker, Richard L. Schilsky, Everett E. Vokes, Mark R. Green

Asian Cancer Institute
Reviving Hopes...

At median follow-up of 74 months differences in survival were non-significant [HR 0.83 (95% CI, 0.64- 1.08, P=0.12)].

Insufficient statistical power, early stop, carboplatin use, stage IB may have influenced the results.

Exploratory analysis showed benefit for patients whose tumors were 4 cm in diameter or larger (HR 0.69).

Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-51

VOLUME 26 · NUMBER 21 · JULY 20 2008
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

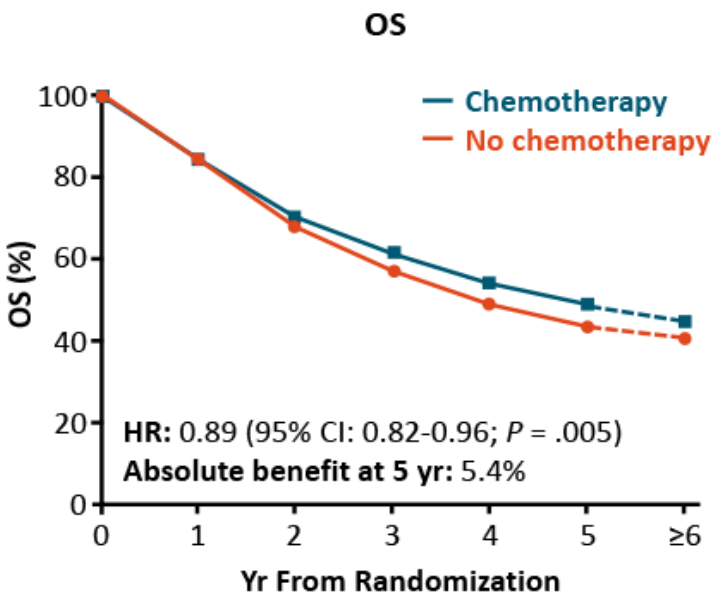
Asian Cancer Institute
Reviving Hopes...

Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group

Jean-Pierre Pignon, Hélène Tribodet, Giorgio V. Scagliotti, Jean-Yves Douillard, Frances A. Shepherd, Richard J. Stephens, Ariane Dunant, Valter Torri, Rafael Rosell, Lesley Seymour, Stephen G. Spiro, Estelle Rolland, Roldano Fossati, Delphine Aubert, Keyue Ding, David. Waller, and Thierry Le Chevalier

Meta-analysis: Lung Adjuvant Cisplatin Evaluation

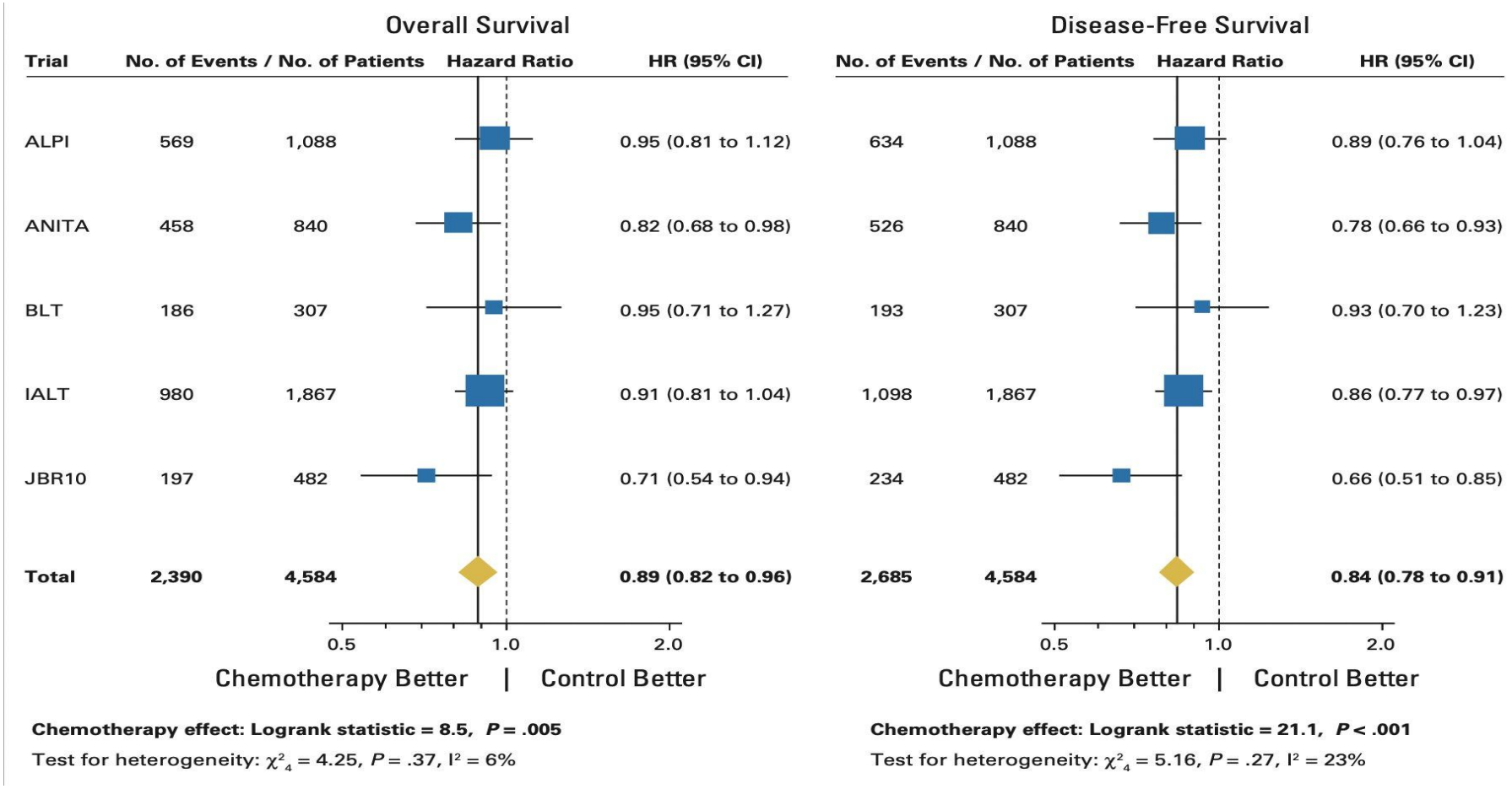
- Pooled individual patient data from 5 studies of adjuvant cisplatin-based chemotherapy for completely resected early-stage NSCLC conducted after 1995 (N = 4584)
  - Studies: ALPI, ANITA, BLT, IALT, JBR10
- Chemotherapy at Yr 5
  - ↓ **6.9%** lung cancer death
  - ↑ **1.4%** noncancer death



Pignon. JCO. 2016;26:3552.

Slide credit: clinicaloptions.com

LACE Meta-analysis



Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.

Asian Cancer Institute
Reviving Hopes...

LACE Meta-analysis : Salient features

❖No heterogeneity of chemotherapy effect.

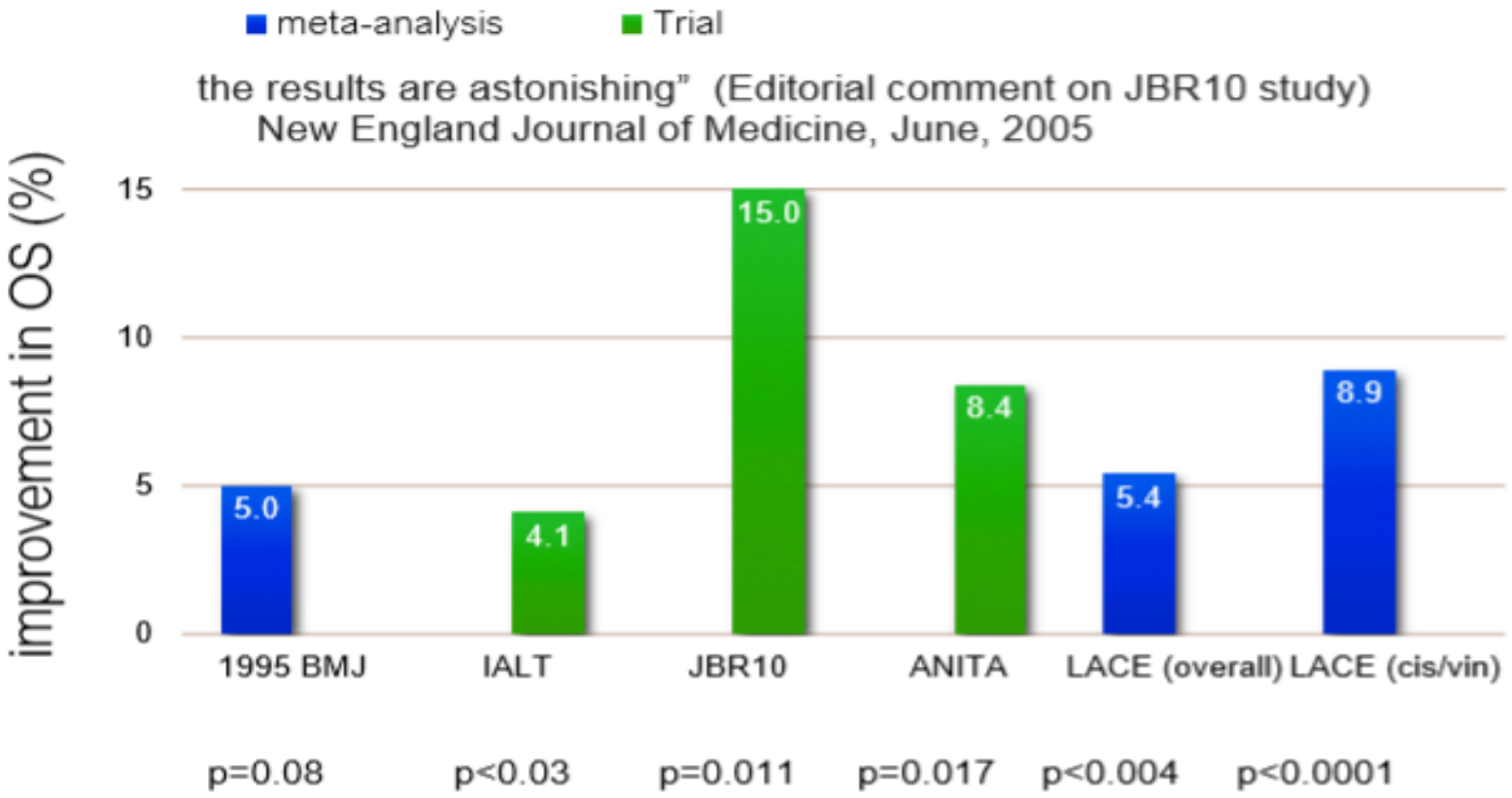
❖Benefit varied with stage (P=0.04) HR being for stage IA 1.4, IB 0.93, II 0.83 and III 0.83.

❖The drug given with cisplatin did not modify the effect of chemotherapy (P=0.11): vinorelbine was higher (0.80), etoposide or other vinca alkaloid 0.92, the rest 0.97.

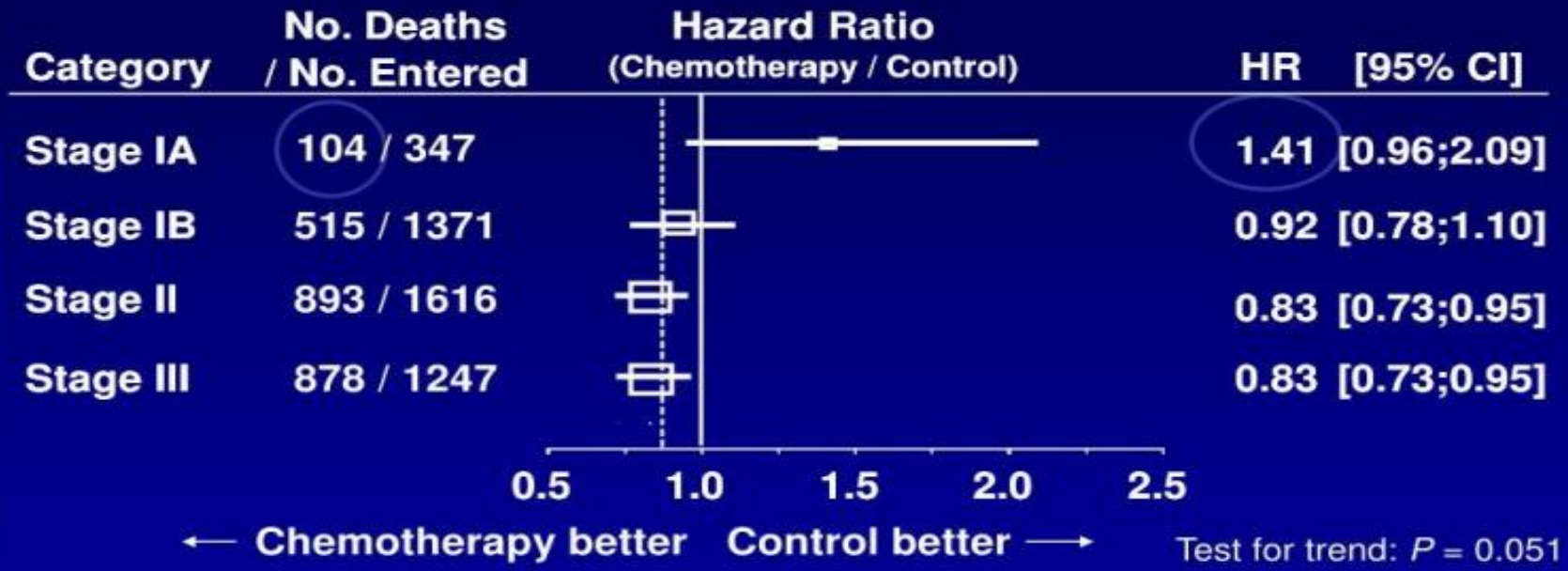
❖Effect of chemotherapy was greater in patients with better performance status and no influence of other variables

Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.

NSCLC - evidence now conclusive….
after 2 decades of research



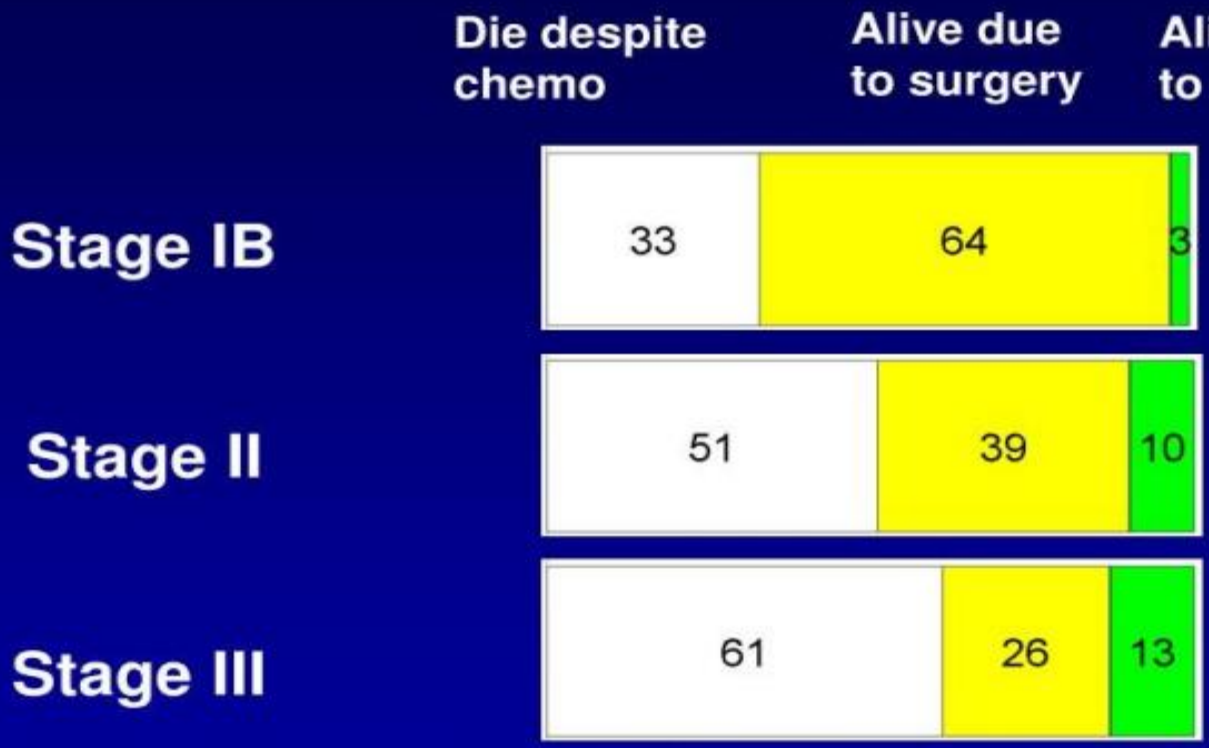
Adjuvant Chemotherapy for NSCLC LACE Analysis by Stage



Adjuvant chemo has greatest benefit for stage II and III and may be detrimental for stage IA

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

Adjuvant Chemo for Stage IB – III NSCLC
Absolute Benefit in 5-Year Survival



Based on HR from LACE meta-analysis and 5YS from ANITA trial
Chemotherapy = 4 months of cisplatin + vinorelbine

Pignon JP et al. *J Clin Oncol.* 2006;24(18S). Abstract 7008; Douillard JY et al. *Lancet Oncol.* 2006:7;719-727

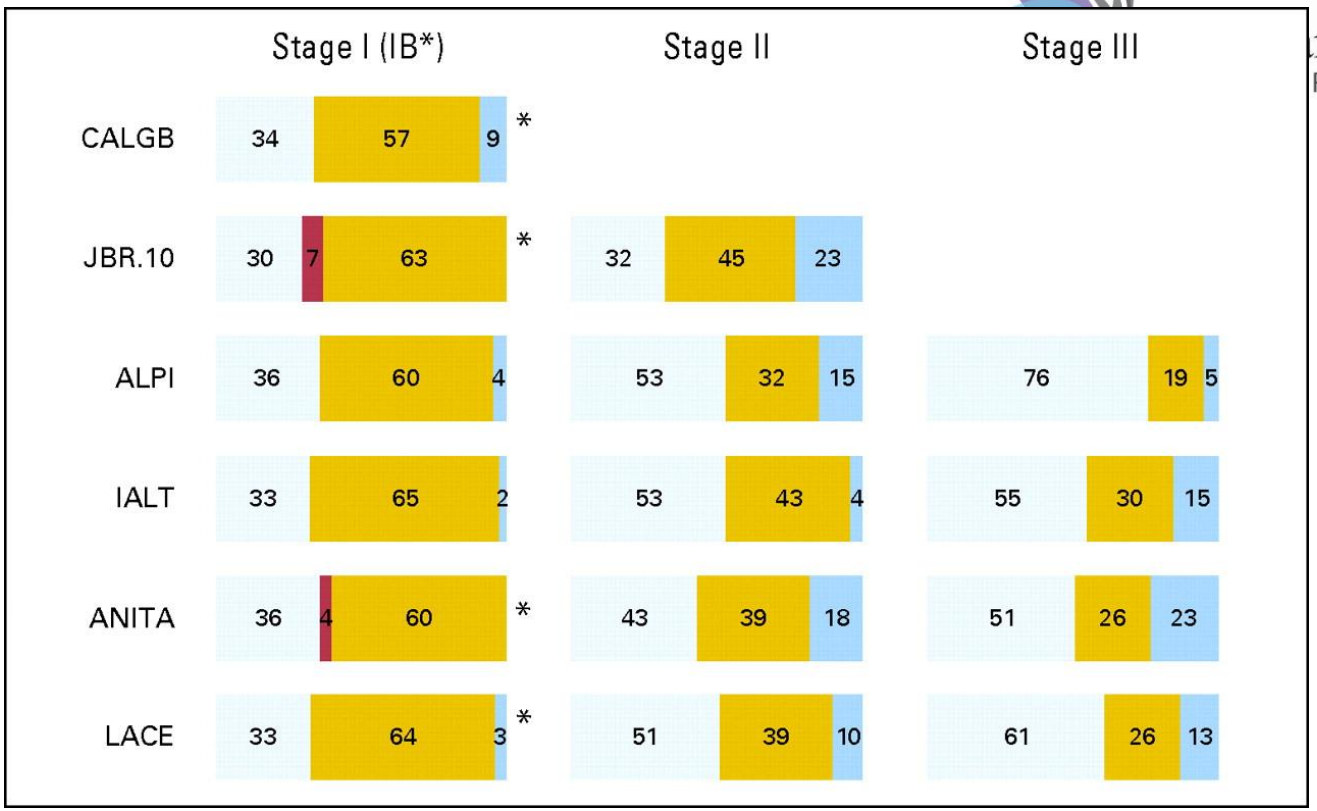


Fig 1. Graphical representation of estimated absolute risk and benefit for 100 patients with non–small-cell lung cancer treated with surgery and adjuvant chemotherapy, based on reported, stage-specific hazard ratio and death rate in the control arm of each clinical trial. (*) Indicates those trials that included only stage IB, ALPI and IALT were open for IA and IB. CALGB, Cancer and Leukemia Group B; NCIC-CTG JBR.10, National Cancer Institute of Canada Clinical Trials Group JBR.10; ALPI, Adjuvant Lung Project Italy; IALT, International Adjuvant Lung Cancer Trial; ANITA, Adjuvant Navelbine International Trialist Association trial; LACE, Lung Adjuvant Cisplatin Evaluation.

Published in: Katherine M.W. Pisters; William K. Evans; Christopher G. Azzoli; Mark G. Kris; Christopher A. Smith; Christopher E. Desch; Mark R. Somerfield; Melissa C. Brouwers; Gail Darling; Peter M. Ellis; Laurie E. Gaspar; Harvey I. Pass; David R. Spigel; John R. Strawn; Yee C. Ung; Frances A. Shepherd; *Journal of Clinical Oncology* 2007 255506-5518.
DOI: 10.1200/JCO.2007.14.1226

Asian Cancer Institute
Reviving Hopes...

Summary / Fading Benefit ?

Table 1 Modern clinical trials of adjuvant chemotherapy in NSCLC

Trial	N	Stage	Chemotherapy	RT	Survival (%) Chemo/Obs	P	Comments
ALPI (6)	1,088	I-IIIA	MVP	±	+1/-	0.59	
IALT (7)	1,867	I-IIIA	CDDP-based	±	44/40	0.03	Not maintained >5 years
BLT (8)	381	I-IIIA	CDDP-based	±	58/60	0.90	At 2 years
CALGB 9633 (9)	344	IB	P + Cb	-	60/58	0.12	
JBR 10 (10)	482	IB-II	VNR + CDDP	-	69/54	0.003	Maintained at 9 years for stage II
ANITA (11)	840	I-IIIA	VNR + CDDP	±	66/44 months (median)	0.02	Maintained at 7 years for stages II-IIIa

ALPI, The Adjuvant Lung Project; IALT, International Adjuvant Lung Cancer Trial; ANITA, the Adjuvant Navelbine International Trialist Association; MVP, mitomycin, ifosfamide, cisplatin; RT, radiotherapy; Obs, observation; Cb, carboplatin; P, paclitaxel; VNR, vinorelbine; NSCLC, non-small cell lung cancer.

Artal Cortés A, Calera Urquizu L, Hernandez Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. Transl Lung Cancer Res 2015;4(2):191-197. doi: 10.3978/j.issn.2218-6751.2014.06.01

Asian Cancer Institute
Reviving Hopes

Toxicity / Cycles

Table 2 Major toxicities reported in the clinical trials of adjuvant chemotherapy in NSCLC

G3-4 toxicity	IALT (%)	JBR.10 (%)	ANITA (%)
Neutropenia	17.5	73	85
Febrile neutropenia	–	7	9
Anemia	–	7	14
Thrombocytopenia	–	1	3
Asthenia	–	15	28
Peripheral neuropathy	–	7	3
Nausea and vomiting	3.3	17	27
Constipation	–	3	5
Treatment-related deaths	0.8	0.8	2
Cisplatin dose intensity	73.8% received; ≥240 mg/m^2	58% received; ≥3 courses	Median 89%
Courses (median/#4)	–	3/45%	4/>50%

Artal Cortés A, Calera Urquizu L, Hernandez Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. Transl Lung Cancer Res 2015;4(2):191-197. doi: 10.3978/j.issn.2218-6751.2014.06.01

Asian Cancer Institute
Reviving Hopes...

Long Term AE's

With the exception of sensory neuropathy and hearing loss, the rest of side effects were recovered and QoL returned to the baseline by 9 months after treatment. [1]

No adverse impact on pulmonary function. [2]

1. Bezjak A, Lee CW, Ding K, et al. Quality-of-life outcomes for adjuvant chemotherapy in early-stage non-small-cell lung cancer: results from a randomized trial, JBR.10. J Clin Oncol 2008;26:5052-9.
2. Kreuter M, Vansteenkiste J, Herth FJ, et al. Impact and safety of adjuvant chemotherapy on pulmonary function in early stage non-small cell lung cancer. Respiration 2014;87:204-10.

Asian Cancer Institute
Reviving Hopes...

QoL

❖Assessed in subset of 357 patients from JBR.10 with baseline assessment

❖Chemotherapy patients had transient worsening QoL (fatigue, nausea and vomiting)

❖Resumed to baseline by 9 months except sensory neuropathy and hearing loss

❖Assessment of all patients showed adjuvant chemotherapy improved quality-adjusted survival despite toxicity of chemotherapy

Bezjak A, Lee CW, Ding K, et al. Quality-of-life outcomes for adjuvant chemotherapy in early-stage non-small-cell lung cancer: results from a randomized trial, JBR.10. J Clin Oncol 2008;26:5052-9.

Role of adjuvant Pemetrexed in nonsquamous NSCLC

Asian Cancer Institute
Reviving Hopes...

Phase II feasibility studies

- NCT00269152: Pem-cis v Pem carbo (n=118), feasibility (4 cycles, >/= 95% planned dose, no grade 3/4 toxicities in >60%) 59 and 50% respectively.
OS for both groups 82-83% at 3yr and 80-83% at 5 yr. (Schmid-Bindert 2015)

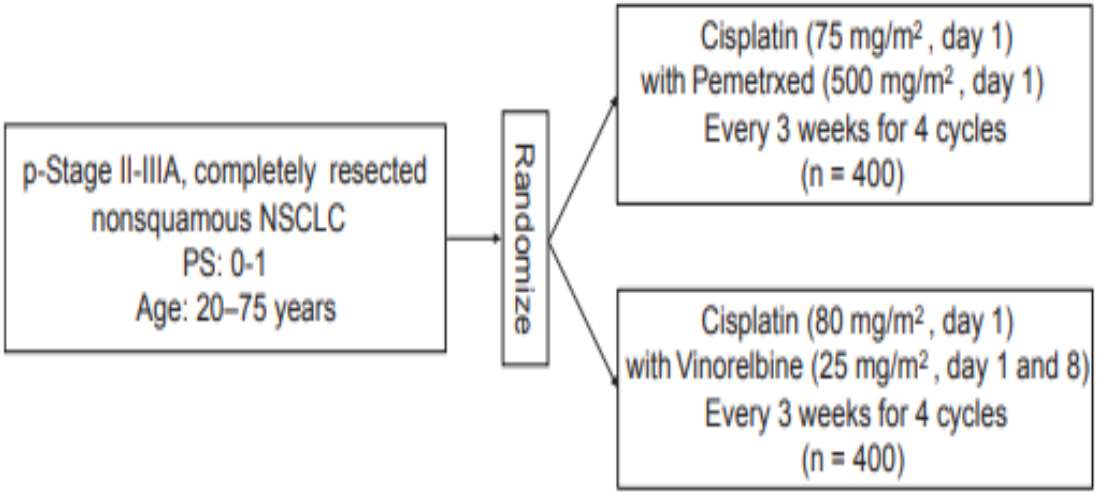
Single arm pem-carbo n=45, 38% squamous. No grade III/IV (Kapanagiou 2009)

Single arm Pem-Carbo , mean TTP 20 months , n=43 (Charpidou 2009)

.

Christian Manegold [1], Gerald Schmid-Bindert, Lothar R Pilz Pemetrexed for the treatment of non-small-cell lung cancer, Expert Rev Anticancer Ther . 2009 Sep;9(9):1195-209.

Figure 1 Japan Intergroup Trial of Pemetrexed Adjuvant Chemotherapy for Completely Resected Nonsquamous Non–Small-Cell Lung Cancer (JIPANG) Study Design



Conclusions: PEM/ CDDP had a similar efficacy to VNR/CDDP with a better tolerability as postoperative adjuvant chemotherapy for Ns-NSCLC patients. A significant interaction for RFS was found between treatment and EGFR mutation status. In patients without EGFR mutation, PEM/Cis seems to be a preferable regimen as the adjuvant chemotherapy.

M.Tsuboi et al, Randomized phase III study of pemetrexed/cisplatin (PEM/Cis) versus vinorelbine /cisplatin (VNR/Cis) for completely resected p-stage II-IIIA non-squamous non-small cell lung cancer (Ns-NSCLC): Outcomes based on EGFR mutation status, Annals of Oncology 30 (Supplement 5): v585–v590, 2019

SYSTEMIC THERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

Preferred (nonsquamous)
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[1]

Preferred (squamous)
- Cisplatin 75 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[2]
- Cisplatin 75 mg/m² day 1, docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[3]

Other Recommended
- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[4]
- Cisplatin 100 mg/m² day 1, vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[5,6]
- Cisplatin 75–80 mg/m² day 1, vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1, etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[5]

Useful in Certain Circumstances
- Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin
- Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[7]
- Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[8]
- Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 for nonsquamous every 21 days for 4 cycles[9]

All chemotherapy regimens listed above can be used for sequential chemotherapy/RT.

Neoadjuvant Systemic Therapy
- Nivolumab 360 mg and platinum-doublet chemotherapy every 3 weeks for 3 cycles[10,*]
  - Platinum-doublet chemotherapy options include:
    - Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
    - Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (non-squamous)
    - Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)

Adjuvant Systemic Therapy
- Osimertinib 80 mg daily[11]
  - Osimertinib for patients with completely resected stage IB–IIIA *EGFR* (*exon 19* deletion, *L858R*) NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
- Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[12]
  - Atezolizumab for patients with completely resected stage IIB–IIIA or high risk stage IIA PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.

References

* Nivolumab in combination with platinum-doublet chemotherapy can be used for patients with resectable (tumors ≥4 cm or node positive) NSCLC in the neoadjuvant setting. If an immune checkpoint inhibitor is used in the pre-operative setting, an immune checkpoint inhibitor should not be used in the adjuvant setting.

Note: This is the NCCN Framework for Resource Stratification of NCCN Guidelines. For definitions of the NCCN Framework™, see page FR-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Asian Cancer Institute
Reviving Hopes...

Thank You