ADVANCES IN NON SURGICAL MANAGEMENT OF LUNG CANCER (NSCLC) (CHEMOTHERAPY & TARGETED THERAPY) REVIEW OF RCT IN LAST 10 YRS

DM SEMINAR
21.08.09

INTRODUCTION

- Lung cancer leading cause of cancer-related mortality
- NSCLC : a systemic disease ,approximately 45 percent of NSCLC present with advanced stage disease
- Most favourable prognostic group,T1N0 disease (up to 25 percent) fail within 5 years after surgery
- Systemic therapy an important component of therapy even in localised disease

SEMINAR OUTLINE

LOCALIZED NON--SMALL-CELL LUNG CANCER

- Early Stage Disease

LOCALLY ADVANCED NSCLC

- Radiation Therapy Alone
- Chemotherapy Followed by Radiation Therapy: Randomized Trials
- Concurrent Chemotherapy and Radiation Therapy
- Chemotherapy Followed by Surgery
- Chemotherapy and Radiation Followed by Surgery
- Future Directions

ADVANCED-STAGE NSCLC

- First-Line Chemotherapy
- Second-Line Therapy
- Future Directions

LOCALIZED NSCLC

- Surgery remains optimal treatment for early stage NSCLC, 5-year survival rates for resected NSCLC without additional treatment range from 23% for Stage IIIA disease to 67% for Stage IA disease

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- Presence of micrometastatic disease at time of resection most likely cause of recurrence
- Adjuvant chemotherapy :a rational treatment ?

ADJUVANT CHEMOTHERAPY

TABLE 1. RECENT CLINICAL TRIALS OF ADJUVANT CHEMOTHERAPY IN NON–SMALL CELL LUNG CANCER

Trial Name	YEAR	Number of Patients	Study Period	Hazard Ratio for Overall Survival		Absolute Improvement* in 5-yr Survival (%)
				95% Confidence Interval	*P* Value	
ECOG 3590	2000	488	1991–1997	0.93 (0.74–1.18)	0.56	0
BLT (13)	2004	381	1995–2001	1.02 (0.77–1.35)	0.90	0
ALPI (14)	2003	1,209	1994–1999	0.96 (0.81–1.13)	0.589	0
IALT (2)	2004	1,867	1995–2001	0.86 (0.76–0.98)	< 0.03	4
CALGB 9633	2004	344	1996–2003	0.62 (0.41–0.95)	0.028	0
ANITA (2)	2004	840	1994–2000	0.80 (0.66–0.96)	0.017	8.6
JBR.10 (4)	2005	482	1994–2001	0.69 (0.52–0.91)	0.04	15

Definition of abbreviations: ALPI = Adjuvant Lung Project Italy; ANITA = Adjuvant Navelbine International Trialist Association; BLT = Big Lung Trial; CALGB = Cancer and Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; IALT = International Adjuvant Lung Cancer Trial.

* Reported for trials that showed statistically significant improvement in survival with adjuvant chemotherapy.

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ADJUVANT CHEMOTHERAPY

Table 14.2 Recent randomized platin-based adjuvant trials and pooled analysis.

Trial	Number of patients	Stage	Chemotherapy	5-yr benefit (%)	Hazard ratio [95% CI]	*p*
ALPI [16]	1209	I-IIIA	MVdP*	3	0.96 [0.81–1.13]	0.589
IALT [17]	1867	I-IIIA	VincaP or EP*	4	0.86 [0.76–0.98]	0.03
BLT [18]	381	I-IIIA	Platin-based*	−2 (2yr)	1.02 [0.77–1.35]	0.90
BR10 [19]	482	IB-II	VnrP	15	0.69 [0.52–0.91]	0.04
CALGB [21]	344	IB	PacCb	2	0.8 [0.6–1.07]	0.1
ANITA [20]	840	IB-IIIA	VnrP*	9	0.8 [0.66–0.96]	0.017
LACE [22]	4584	I-IIIA	Cisplatin-based*	5	0.89 [0.82–96]	0.004

*Optional adjuvant radiotherapy.

EP, etoposide/cisplatin; ALPI, Adjuvant Lung Project Italy; MVdP, mitomycin/vindesine/cisplatin; IALT, International Adjuvant Lung Trial; VincaP, vinorelbine, vindesine, or vinblastine/cisplatin; BLT, Big Lung Trial; BR10: from NCIC-CTG, National Institute of Canada Clinical Trials Group; VnrP, vinorelbine/cisplatin; CALGB, Cancer and Leukemia Group B; PacCb, paclitaxel/carboplatin; ANITA, Adjuvant Navelbine International Trialist Association; LACE, Lung Adjuvant Ciplatin Evaluation.

Proc Am Thorac Soc .Vol 6. pp 194–200, 2009

Metaanalysis of recent randomized adjuvant cisplatin-based chemotherapy

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

VOLUME 26 · NUMBER 21 · JULY 20 2008

JOURNAL OF CLINICAL ONCOLOGY

Table 1. Trial Description

Trial Name	Inclusion Criteria	Chemotherapy (No. of cycles, dose of cisplatin by cycle, daily dose × No. of doses for other drugs)	Radiotherapy	Inclusion Period	No. of Patients Included
JBR10	pT2pN0* or pT1-2pN1	4 cycles, cisplatin (50 × 2) mg/m² Vinorelbine 25 mg/m² × 16	No radiotherapy	1994-2001	482
Adjuvant Lung Cancer Project Italy	Stage I, II, IIIA	3 cycles, cisplatin 100 mg/m² Mitomycin 8 mg/m² × 3, vindesine 3 mg/m² × 6	Optional After chemotherapy	1994-1999	1,088
Adjuvant Navelbine International Trialist Association 01	Stage I, II, IIIA	4 cycles, cisplatin 100 mg/m² Vinorelbine 30 mg/m² × 16	Optional for pN+ After chemotherapy	1994-2000	840
International Adjuvant Lung Trial	Stage I, II, III	3 cycles, cisplatin 100 or 120 mg/m² or 4 cycles, cisplatin 80 or 100 mg/m² Vindesine 3 mg/m² × 6-8, or Vinblastine 4 mg/m² × 6-8, or Vinorelbine 30 mg/m² weekly × 13, or Etoposide 100 mg/m² × 9-12	Optional according to pN After chemotherapy	1995-2001	1,867
Big Lung Trial	Stage I, II, III	3 cycles, cisplatin 80 mg/m² (biotherapies) or 50 mg/m² (tritherapies) Vindesine 3 mg/m² × 6, or Vinorelbine 30 mg/m² × 6, or Mitomycin 6 mg/m² × 3 and ifosfamide 3 g/m² × 3, or Mitomycin 6 mg/m² × 3 and vinblastine 6 mg/m² × 3	Optional After chemotherapy	1995-2001	307†

Abbreviation: JBR10, National Cancer Institute of Canada Clinical Trial Group trial JBR10.
*Pathologic tumor (pT) and nodal (pN) stage.
†Patients with incomplete resection (n = 61) or neoadjuvant chemotherapy (n = 13) were excluded.

LACE : RESULTS

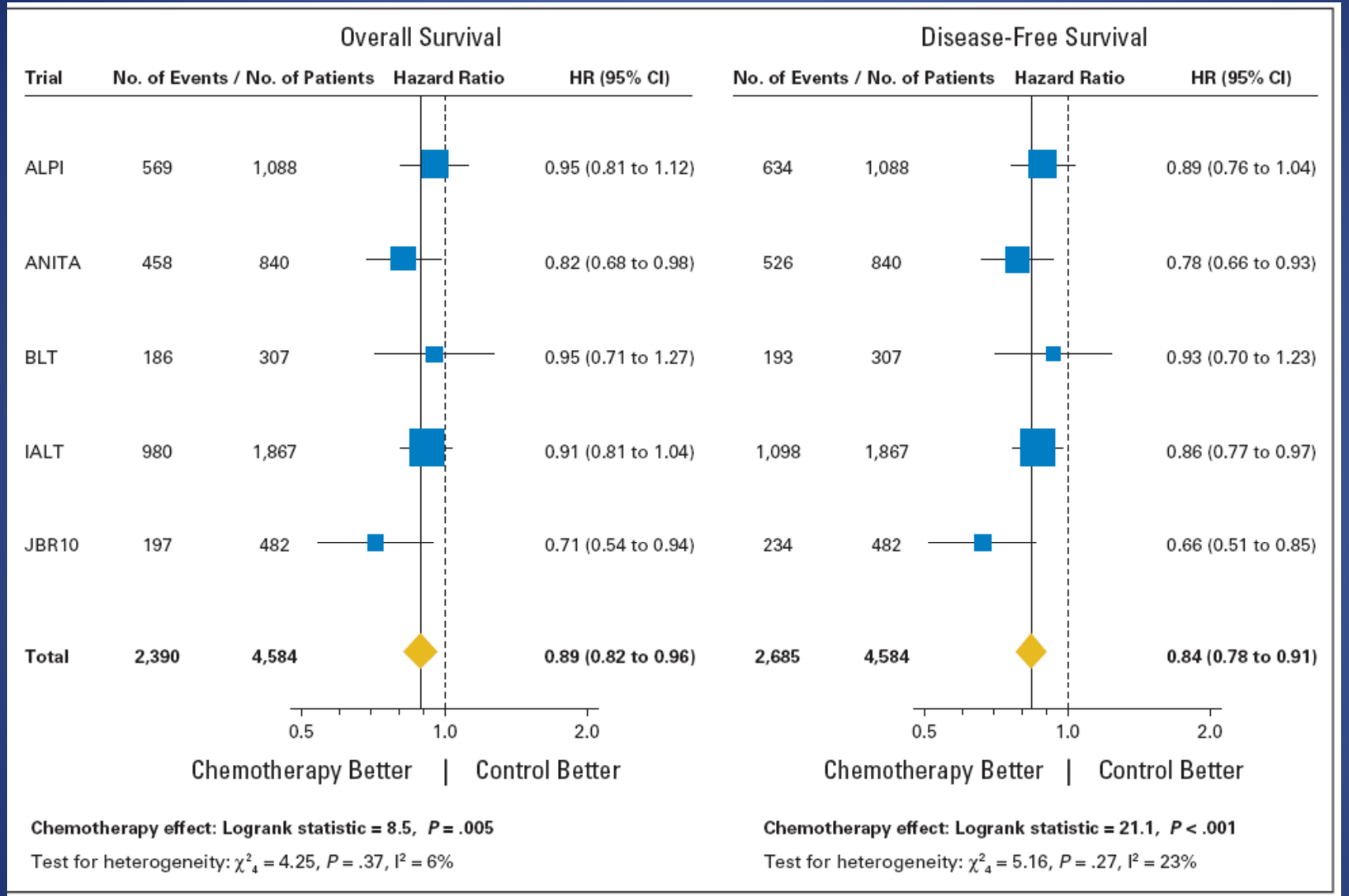

Fig 1. (A) Overall survival (OS): hazard ratio (HR) of death with chemotherapy versus control (no chemotherapy). (B) Disease-free survival (DFS): HR of recurrence or death with chemotherapy versus control. HR for individual trials and overall effect are given with 95% CIs. The horizontal scale used is a logarithmic scale. ALPI, Adjuvant Lung Cancer Project Italy; ANITA, Adjuvant Navelbine International Trialist Association 01; BLT, Big Lung Trial; IALT, International Adjuvant Lung Trial; JBR10, National Cancer Institute of Canada Clinical Trial Group trial JBR10.

OS (5.4% absolute benefit at 5 years) and DFS (5.8% benefit)

JCO 2008

LACE: RESULTS

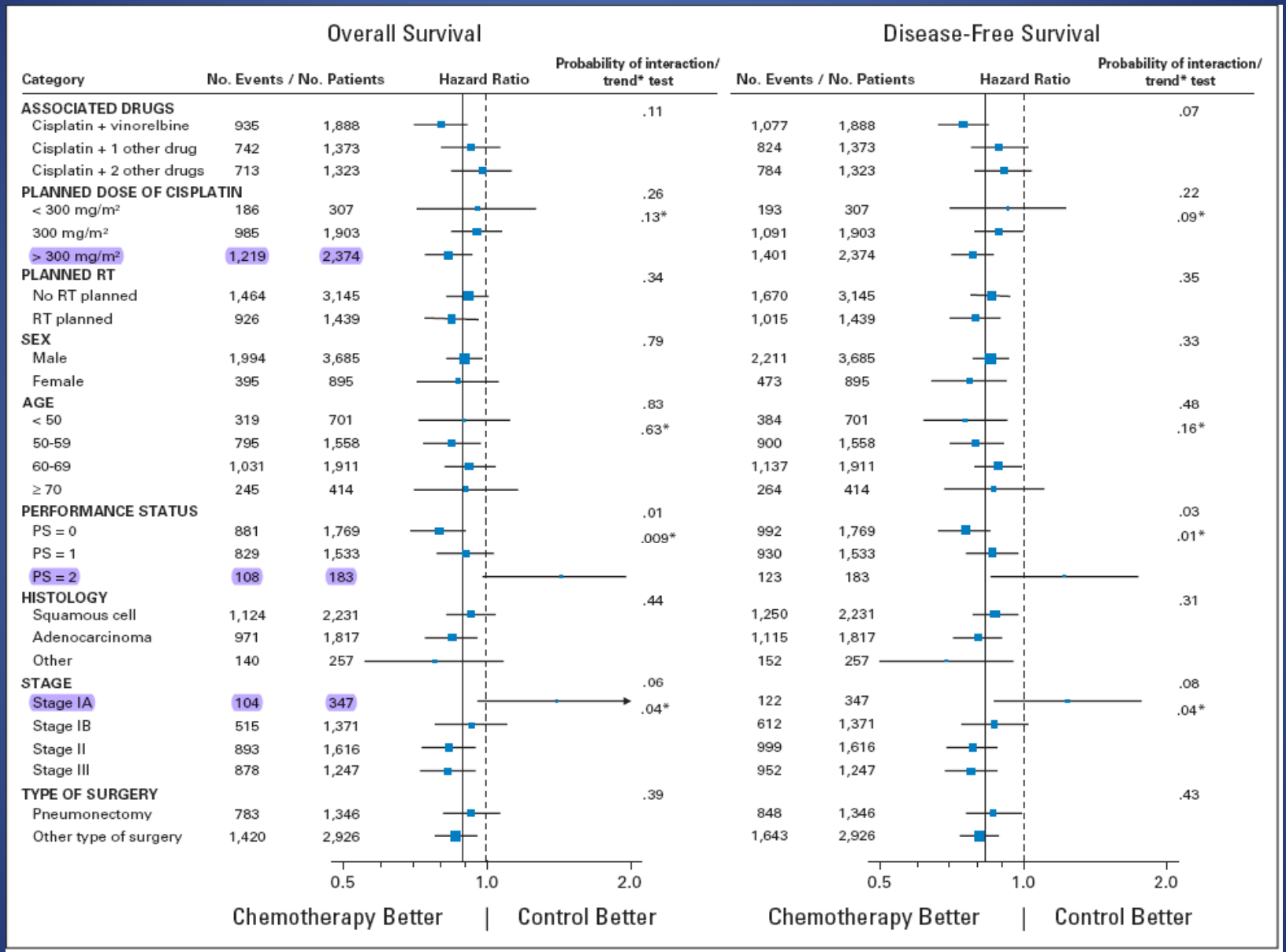

Fig 3. (A) Overall survival (OS): hazard ratio (HR) of death with chemotherapy versus control (no chemotherapy) by trial or baseline patient characteristic. (B) Disease-free survival (DFS): HR of recurrence or death with chemotherapy versus control by trial or baseline patient characteristic. RT, radiotherapy; PS, performance status.

JCO 2008

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Magnitude of benefit of adjuvant chemotherapy for non-small cell lung cancer: Meta-analysis of randomized clinical trials

Emilio Bria[a,*], Richard J. Gralla[b], Harry Raftopoulos[b], Federica Cuppone[a], Michele Milella[a], Isabella Sperduti[c], Paolo Carlini[a], Edmondo Terzoli[a], Francesco Cognetti[a], Diana Giannarelli[c]

[a] *Department of Medical Oncology, Regina Elena National Cancer Institute, Roma, Italy*
[b] *Hematology and Oncology, Monter Cancer Center, Northshore-LIJ Health System, Lake Success, NY, USA*
[c] *Biostatistics, Regina Elena National Cancer Institute, Roma, Italy*

Author	Arms	Number (patients)	Stage	Median FU	HR for OS	*p*
NSCLC–CG-MA* [6]	Control vs. Cis	688 (706)	I–III	NR	0.87	0.08
Keller et al. [10]	RT vs. Cis-RT	242 (246)	II–IIIA	44	0.93	0.56
Xu et al. [18]	Control vs. Cis	35 (35)	I–III	NR	NR	<0.025
Roselli et al. [13]	Control vs. Cis	70 (70)	IB	>70	NR	0.02
Nagakawa et al. [12]	Control vs. Cis	48 (47)	II–IIIA	91	NR	0.52
Scagliotti et al. [14]	Control vs. Cis	540 (548)	I–IIIA	64.5	0.96	0.58
Arriagada et al. [7]	Control vs. Cis	935 (932)	I–IIIA	56	0.86	<0.03
Tada et al. [15]	Control vs. Cis	60 (59)	IIIA	NR	NR	0.89
Waller et al. [16]	Control vs. Cis	189 (192)	I–III	64.5	1.02	0.90
Strauss et al. [19]	Control vs. Carbo	171 (173)	IB	57	0.80	0.10
Imaizumi et al. [9]	Control vs. Cis	50 (50)	I	78	0.46	0.045
Winton et al. [17]	Control vs. Cis	239 (243)	IB–II	NR	0.70	0.012
Douillard et al. [8]	Control vs. Cis	433 (407)	IB–IIIA	76	0.80	0.017

RESULTS

- Significant benefit on both overall and disease-free survival
- Magnitude of the benefit not large. Overall, 3–4% absolute benefit in survival
- 24–39 patients need to be treated for one to benefit
- Most studies have under-representation of older patients

The known and the unknown

Which stages should be treated?

- **Stage IA**
- BLT, ALPI, and IALT only cisplatin-based chemotherapy trials to include stage IA disease
- LACE pooled analysis : detrimental effect in that subgroup ,patients treated by the toxic mitomycin C/vindesin/cisplatin regimen
- Nevertheless, adjuvant cisplatin-based chemotherapy not a standard of care in stage IA disease

The known and the unknown

Stage IB

- Statistically negative CALGB study ,only large platin-based adjuvant trial focusing on stage IB disease
- Subgroup analysis of JBR10 and ANITA trials, no benefit was observed for patients with stage IB disease
- LACE pooled analysis, benefit for adjuvant chemotherapy reported but insufficient to recommend it as a standard (> 4 cm)
- Oral uracil/tegafur (UFT) in adjuvant treatment of NSCLC studied in Japan in several clinical trials

N Engl J Med 2004;350:1713-21.
Proc Am Thorac Soc .Vol 6. pp 194–200, 2009

- STAGE II
- Data for use of adjuvant cisplatin-based chemotherapy in stage II NSCLC strong
- JBR.10, and ANITA studies found significant benefit for the use of adjuvant chemotherapy
- LACE meta-analysis, a 27% reduction in the risk of death(HR = 0.83; 95% CI 0.73-0.95) found in 1616 stage II patient subset

ADJUVANT CHEMOTHERAPY : CURRENT STATUS

Table 1 Results of adjuvant chemotherapy in patients with early-stage NSCLC [2–6]

Trial	Stage IA	Stage IB	Stage II	Stage IIIA
ALPI [2]	Negative	Negative	Negative	Negative
IALT [3]	Negative	Negative	Negative	Positive
NCIC [4]	Not Tested	Negative	Positive	Not tested
CALGB [5]	Not tested	Initially positive* Subsequently negative	Not tested	Not tested
ANITA [6]	Not tested	Negative	Positive	Positive

*Early data.

ALPI, Adjuvant Lung Cancer Project Italy; ANITA, Adjuvant Navelbine International Trialists Association; CALGB, Cancer and Leukaemia Group B; IALT, International Adjuvant Lung Cancer Trial; NCI-C, National Cancer Institute of Canada.

Lung Cancer (2007) **57 (Supplement 2), S6---S11**

LOCALLY ADVANCED NSCLC :STAGE III A & B

- 40% of individuals with locally advanced disease (stage III), including resectable and unresectable tumours Cancer J Clin 2006; 56: 106 - 30.
- Stage III includes heterogeneous group, ranging from T3 N1 to T4 N3 and prognosis is extremely variable but all have in common absence of disease outside of chest
- Some of these lesions are eminently resectable, others marginally resectable, and others out of realm of resectability
- Distinction between IIIA and IIIB lesions important, since prognosis significantly worse for latter lesions

TO CUT OR NOT TO CUT

TABLE 1. Clinically Distinct Subsets within Stage III Non-small Cell Lung Cancer.

Stage	TNM Classification	Description
Stage IIIA	T3 N1	Peripheral lesion with chest wall invasion or tumor < 2 cm distal to carina
	T1–3 N2*	Prognosis and therapy defined by N2 status (ipsilateral mediastinal nodes)
Stage IIIB	T1–4 N3	Prognosis and therapy largely defined by N3 disease (contralateral mediastinal, supraclavicular nodes)
	T4 N0–2	Locally invasive primary tumor (T4) and no malignant pleural effusion; no contralateral or supraclavicular nodes
	T4 N0–3	Malignant pleural effusion (T4)

RESECTABLE

POTENTIALLY RESECTABLE

TNM, tumor–node–metastasis.
*Stage IIIA(N2) can be further subdivided according to the extent of nodal involvement (microscopic, minimal or bulky N2 disease) and planned surgical resection (lobectomy versus pneumonectomy).

- Whether NSCLC individuals with IIIA (N2) cancer should undergo surgical resection still controversial
- Non-bulky mediastinal node involvement as candidates for surgery
- Selected T4 patients with N0 or minimal N1 disease (IIIB) considered amenable for surgical resection, including patients with satellite nodules in same lobe or those with limited involvement of carina

(J Thorac Oncol. 2007; suppl. 2: S77–S85)

STAGE III A (N2) NON-SMALL CELL LUNG CANCER

Table 1—*Subsets of Stage IIIA(N_2)

Subset	Description
$IIIA_1$	Incidental nodal metastases found on final pathology examination of the resection specimen
$IIIA_2$	Nodal (single station) metastases recognized intraoperatively
$IIIA_3$	Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)
$IIIA_4$	Bulky or fixed multistation N2 disease

UNRESECTABLE

ACCP : CHEST 2007; 132:243S–265S)

Incidental N2 Disease (Stage IIIA1–2)

Adjuvant Radiotherapy

- postoperative radiation controversial and not recommended for routine use because of lack of prospective RCT data evaluating efficacy
- PORT metanalysis : subgroup analyses showed adverse effect greatest for patients with N0-N1, while no clear evidence of adverse effect on survival for patients with N2 disease

Lancet 1998;352:257–263

- Surveillance Epidemiology and End Results (SEER) database showed no evidence of overall survival benefit with use of PORT in N0-N1 disease
- However, SEER analysis showed survival benefit with use of PORT in N2 disease

J Clin Oncol 2006;24:2998–3006

STAGE III A1-2

- An unplanned analysis of patients in ANITA trial that received radiation treatment showed N2 disease had survival benefit with PORT
- The Lung Adjuvant Radiation Trial (Lung- ART) is an ongoing phase III trial in which patients with resected N2 disease will be randomized to PORT and no PORT and stratified by use of postoperative chemotherapy

Proc Am Thorac Soc Vol 6. pp 194–200, 2009

ADJUVANT RADIOTHERAPY :CURRENT STATUS

Postoperative radiotherapy for non-small cell lung cancer (Review)

Cochrane Database of Systematic Reviews, Issue 3, 2009 (

PORT detrimental to patients with early stage completely resected non-small cell lung cancer and not be used in the routine treatment of such patients.

The role of PORT in treatment of N2 tumours not clear and may justify further research

STAGE IIIA 1-2

- *Adjuvant Combination Chemoradiotherapy*

Table 4—*Randomized Controlled Trials of Surgery Plus Adjuvant Chemoradiotherapy vs Surgery Plus Adjuvant Radiotherapy

Source	Year	Patients, No.	Stage	Chemotherapy Radiotherapy Regimens	Disease-Free Survival	Long-term Survival Surgery-XRT vs Surgery-XRT/Chemotherapy, %
Lad et al[44]	1988	164	II–III	CAP40 Gy (split course)	Chemo favored (p = 0.004)	54/68 (p = 0.1); 1 yr
Sawamura et al[45]	1988	52	II–III	Tegafur-CDDP 50 Gy	NS	NS
Pisters et al[46]	1994	72	III	Vd-CDDP 40 Gy	NS	44/31 (p = 0.42); 2 yr
Dautzenberg et al[47]	1995	267	I–III	A-C-CCNU-CDDP-V 60 Gy	NS	12/13 (p = 0.68); 10 yr
Keller et al[16] (Intergroup E3590)	2000	488	II–IIIA	CDDP-VP-16 50.4 Gy	NS	39 mo/38 mo (p = 0.56 median)

ACCP : CHEST 2007; 132:243S–265S

Potentially Resectable N2 Disease (Stage IIIA3)

NEOADJUVANT CHEMOTHERAPY

- Specific strategy of using drug treatment at earliest time possible
- Systemic treatment of occult microscopic metastatic disease at earliest possible time
- Reduction in the primary tumor mass lead to more radical and smaller resections or even render borderline unresectable lesions resectable
- Better tolerated than adjuvant administration, resulting in higher rate of treatment compliance (45–60% VS 80%)

Curr Opin Oncol 19:92–97. 2007

Neoadjuvant chemotherapy : Evidence

Randomised trials of preoperative platinum-based chemotherapy in patients with stage IB-IIIA non-small cell lung cancer

Trial	Stage	No. of patients	Treatment	Median survival (months)	5-year survival (%)	p-Value for median survival
Rosell et al. 1994	IIIA	60	MIC × 3 cycles → surgery	26	17	p < 0.001
			Surgery alone	8	0	
Pass et al. 1992	IIIA	27	EP × 2 cycles → surgery → EP	28.7	NR	p = 0.095
			Surgery alone	15.6		
Roth et al. 1998	IIIA	60	CEP × 6 cycles → surgery	21	36	p = 0.056
			Surgery alone	14	15	
DePierre et al.[26] 2002	IB-IIIA	355	MIP × 2 cycles → surgery → MIP	37	44[a]	p = 0.15
			Surgery	26	35[a]	
Nagai et al. 2003	IIIA-N2	62	CV × 3 cycles	17	10	p = 0.53
			Surgery	16	22	
Pisters et al. 2005	IB-IIIA	354	CP × 3 → surgery	42	68[b]	HR = 0.88
			Surgery	37	64[b]	p = 0.47

a Reported as 4-year survival rate.

b Reported as 2-year survival rate.

CEP = cyclophosphamide, etoposide, cisplatin; **CP** = carboplatin, paclitaxel; **CV** = cisplatin, vindesine; **EP** = etoposide, cisplatin; **HR** = hazard ratio; **MIC** = mitomycin, ifosfamide, cisplatin; **MIP** = mitomycin, ifosfamide, cisplatin; **NR** = not reported. → indicates followed by.

Drugs 2007; 67 (3): 321-332

Role of preoperative chemotherapy for non-small-cell lung cancer: A meta-analysis

Haruhiko Nakamura[a,*], Norihito Kawasaki[a], Masahiko Taguchi[a], Kazuyuki Kabasawa[b]

Lung Cancer (2006) 54, 325–329

alone. The combined survival differences at 1 and 3 years time point were significant, while the difference at 5 years after resection was not significant. When only the 122 stage IIIA patients were analyzed, none of the HR at any time point was significant. In conclusion, the present meta-analysis suggests that the benefit of preoperative chemotherapy for patients with NSCLC is unclear, especially for stage IIIA patients.

In NSCLC patients with N2 disease identified preoperatively (IIIA3), induction therapy followed by surgery is not recommended except as part of a clinical trial 1 C ACCP : CHEST 2007

RECENT TRIALS

Table V. Ongoing trials of preoperative chemotherapy or chemoradiotherapy in patients with non-small cell lung cancer[47]

Trial	Clinical stages	Chemotherapy	Accrual goal
NATCH	IA (>2.5cm), IB, II, IIIA (T3N1)	CP → surgery	624
		Surgery → CP	
		Surgery alone	
IFCT-0002	I, II	CP × 4 cycles → surgery	520
		CP × 2 cycles → surgery → CP × 2	
		GC × 4 cycles → surgery	
		GC × 2 cycles → surgery → GC × 2	
MRC-LU22	Any resectable	MIP, MVP, CP, GC	600
RTOG 0412/SWOG 0332	Stage IIIA-N2	CD → surgery	574
		CD/TRT[a] → surgery	

a TRT will be given concurrently with chemotherapy.

CD = cisplatin, docetaxel; **CP** = carboplatin, paclitaxel; **GC** = gemcitabine, cisplatin; **IFCT** = Intergroupe Francophone de Cancerologie Thoracique; **MIP** = mitomycin, ifosfamide, cisplatin; **MRC** = Medical Research Council; **MVP** = mitomycin, vinblastine, cisplatin; **NATCH** = NeoAdjuvant Taxol Carboplatin Hope; **RTOG** = Radiation Therapy Oncology Group; **SWOG** = Southwest Oncology Group; **TRT** = thoracic radiotherapy. → indicates followed by.

Drugs 2007; 67 (3): 321-332

Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review

LANCET 2007

- largest RCT of neo-adjuvant chemotherapy in operable NSCLC : shows no evidence of an overall survival benefit for neo-adjuvant chemotherapy.
- Combining this result with all the other RCT of neo-adjuvant chemotherapy suggests a relative benefit of 12% for neo-adjuvant chemotherapy, equivalent to an absolute survival benefit of 5% at 5 years

A phase III randomized trial of surgery alone, or preoperative (PREOP) paclitaxel/carboplatin (PC) followed by surgery, or surgery followed by adjuvant (ADJ) PC in early stage non-small cell lung cancer (NSCLC): NATCH follow-up data

E. Felip, B. Massuti, G. Alonso, J.L. González-Larriba, C. Camps, D. Isla, J.A.Maestre, J.M.R. Paniagua, T. Overbeck, E. Costas, J.J. Sánchez, R. Rosell

On behalf of the Spanish Lung Cancer Group

13th World Conference on Lung Cancer, San Francisco, August 3, 2009

UNRESECTABLE NSCLC
(STAGE III A 4 & III B)

Combining chemotherapy and radiotherapy

Rationale

- Toxicity independence
- Normal tissue protection
- Spatial cooperation
- Tumor response enhancement
- Clinically, empirical rationale for combining radiation therapy and chemotherapy is all-too frequent failure of either modality to effect a cure

Induction chemotherapy before radiotherapy

Trials of sequential chemotherapy and radiation therapy for locally advanced nonsmall cell lung cancer.

First author, year [ref.]	Number of patients	RT (Gy)	CT	MST (mo)	LRC (%)		OS (%)	
					3 yr	5 yr	3 yr	5 yr
Dillman *et al.*, 1996 [13]	77	60	—	9.7	6	5	11	7
	79	60	PV	13.8	18	6 ($p = 0.026$)	23	19 ($p = 0.012$)
Brodin *et al.*, 1996 [14]	164	56 (SC)	—	N/R	N/R	3 (4 yr)	6	1.4
	163	56 (SC)	CE	N/R	N/R	7 (4 yr) ($p = 0.07$)	13	3 ($p = 0.16$)
Morton *et al.*, 1991 [15]	58	60	—	9.6	N/R	N/R	N/R	7
	56	60	MACC	10.4	N/R	N/R	N/R	5
Le Chevalier *et al.*, 1992 [16]	177	65	—	10.0	17 (1 yr)	N/R	4	3
	176	65	VCPC	12.0	15 (1 yr)	N/R	12	6 ($p < 0.02$)
Sause *et al.*, 2000 [17]	149	60	—	11.4	N/R	N/R	11	5
	151	60	PV	13.2	N/R	N/R	17	8
	152	69.6 (bid)	—	12	N/R	N/R	14	6 ($p = 0.04$)

CT, chemotherapy; LRC, local–regional control; MACC, methotrexate, doxorubicin, cyclophosphamide, lomustine; MST, median survival time; N/R, not reported; OS, overall survival; PV, cisplatin, vinblastine; RT, radiation therapy; SC, split course; bid, 1.2 Gy twice daily; VCPC, vindesine, cyclophosphamide, cisplatin, lomustine.

Curr Opin Pulm Med :2007;13:297–304.

CONCURRENT CHEMORADIOTHERAPY

- Many chemotherapeutic agents active in NSCLC possess radiosensitizing properties, thereby improving probability of local control
- Chemotherapy administered concurrent with thoracic radiation may act systemically and potentially eradicate distant micrometastases
- Concurrent chemoradiotherapy leads to 14%reduction in risk of death at two years compared to sequential chemoradiotherapy, and 7% reduction compared to radiotherapy alone.

Cochrane Database of Systematic Reviews, Issue 3, 2009

SEQUENTIAL VS CONCURRENT

Phase III trials of concurrent vs. sequential chemoradiotherapy in stage III nonsmall cell lung cancer

Study	No. patients	Regimen	Outcome
Furuse *et al.* 1999	320	PVdM + RT (56 Gy split course) vs. PVdM → RT (56 Gy; continuous)	median survival: concurrent 16.6 months; sequential 13.3 months ($P = 0.03998$) 2-year survival: concurrent 34.6%; sequential 27.4% 5-year survival: concurrent 15.8%; sequential 8.9%
Radiation Therapy Oncology Group 9410 2003	610	PVi → RT (60 Gy) vs. PVi + RT (60 Gy) vs. HF-x-RT (69.6 Gy)	median survival: sequential 14.6 months; concurrent (daily RT) 17 months ($P = 0.046$); concurrent HF-x-RT 15.6 months (NS) 4-year survival: sequential 12%; concurrent (daily RT) 21% ($P = 0.046$); concurrent HF-x-RT 17% (P = NS)
GLOT-GFPC NPC 95-01 2001	212	PE + RT (66 Gy) → PN vs. PN → RT (66 Gy)	median survival: sequential 13.8 months; concurrent 15 months (NS) 2-year survival: sequential 23%; concurrent 35% (NS)
Zatloukal *et al.* 2004	102	PN + RT (60 Gy) vs. PN → RT (60 Gy)	median survival: sequential 12.9 months; concurrent 16.6 months ($P = 0.023$) 3-year survival: sequential 9.5%; concurrent 18.6%

Curr Opin Pulm Med :2007;13:297–304.

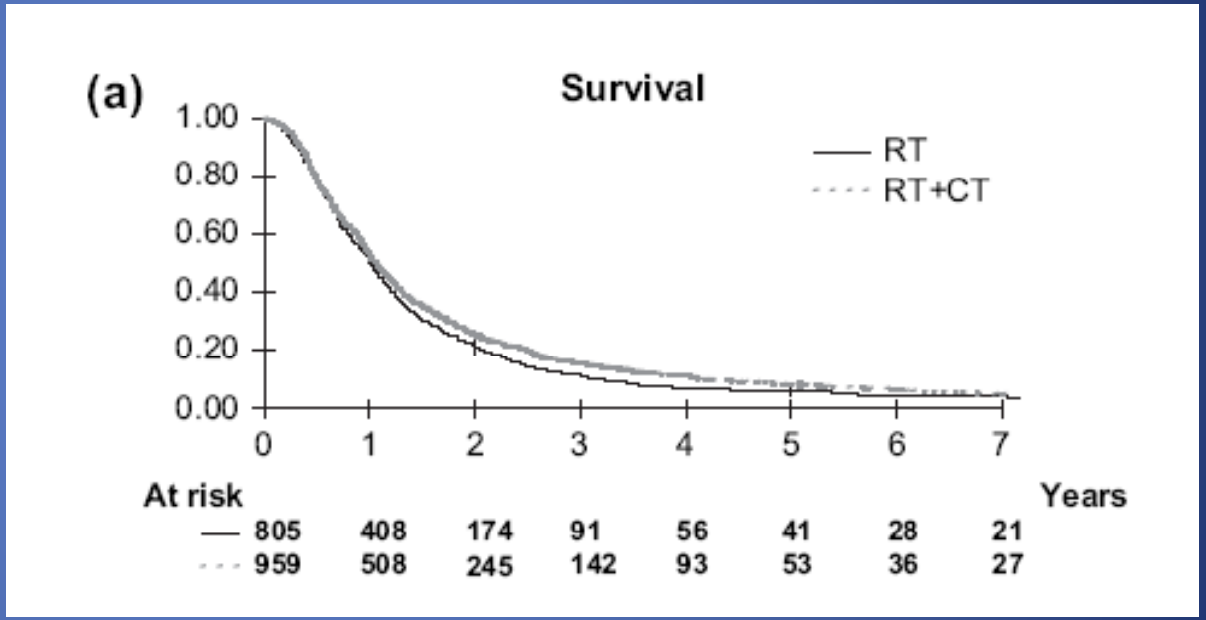
original article

Annals of Oncology 17: 473–483, 2006
doi:10.1093/annonc/mdj117

Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients

A. Aupérin[1*], C. Le Péchoux[2], J. P. Pignon[1], C. Koning[4], B. Jeremic[5], G. Clamon[6], L. Einhorn[7], D. Ball[8], M. G. Trovo[9], H. J. M. Groen[10], J. A. Bonner[11], T. Le Chevalier[3] & R. Arriagada[2,12]
On behalf of the Meta-Analysis of Cisplatin/carboplatin based Concomitant Chemotherapy in non-small cell Lung Cancer (MAC3-LC) Group

- HR : 0.89 : absolute benefit of CRT VS RT of 4% at 2 years and 2.2% at 5 years, increasing respectively 2- and 5-year survival rates from 21.4% to 25.4%, and from 6.0% to 8.2%
- Effect of concomitant CRT greater in stage IIIa than in stage IIIb, both for survival (HR = 0.81 versus 1.01, P = 0.053), and for event-free survival (HR = 0.76 versus 1.02, P = 0.047)
- Benefit of concomitant CRT also seemed to be greater in older patients(> 70 YRS-III B)



Concomitant platin-based CRT might moderately improve survival. However, available data insufficient and treatment designs too heterogeneous to reliably confirm this or to accurately define size of such potential treatment benefit and optimum schedule of chemotherapy

Concurrent chemoradiotherapy in non-small cell lung cancer (Review)

THE COCHRANE COLLABORATION®

- Fourteen randomised studies (including 2393 patients) of concurrent CRT versus radiotherapy alone met inclusion criteria
- Reduction in risk of death at two years (relative risk (RR) 0.93; 95% CI 0.88 to 0.98; P = 0.01).
- Improvements in two-year locoregional progression-free survival (RR 0.84; 95%CI 0.72 to 0.98; P = 0.03) and progression-free survival at any site (RR 0.90; 95%CI 0.84 to 0.97; P = 0.005) seen in those receiving concurrent CRT
- Subgroup analysis : possibility of greater benefit from once daily fractionation regimen of radiotherapy or higher total chemotherapy dose
- Incidence of acute oesophagitis, neutropenia and anaemia significantly increased by concurrent chemoradiotherapy

Cochrane Database of Systematic Reviews, Issue 3, 2009

Trimodality treatment, chemoradiation followed by surgery

Randomized phase III trials of trimodality treatment in stage III nonsmall cell lung cancer

Study	No. patients	Stage	Regimen	Outcome
Intergroup 0139 2005	429	IIIA (n2)	PE + RT (45 Gy) + surgery PE + RT (45 Gy) + RT (61 Gy)	complete resection rate: 88% pCR: 18% nodal clearance: 46% median survival: CRT → surgery 22.1 months; CRT 21.7 months (NS)
German Lung Cancer Cooperative Group 2004	558	IIIA IIIB	3 × PE + CVd + HF-x-RT (45 Gy) → surgery 3 × PE + surgery → RT (54 Gy)	Complete resection rate in both arms: 45% 3-year survival; CT → CRT → surgery 26%; CT → surgery → RT 25% (NS) 3-year PFS: CT → CRT → surgery 18%; CT → surgery → RT 20% (NS)

[Reprinted with permission from the American Society of Clinical Oncology. Farray D, Mirkovic N, Albain K. Multimodality therapy for stage III non-small-cell lung cancer. J Clin Oncol 2005; 23(14):3257–3269]. P, cisplatin; E, etoposide; C, carboplatin; Vd, vindesine; pCR, pathologic complete response; CT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy; HF-x-RT, hyperfractionated radiotherapy; NS, not significant; PFS, progression-free survival.

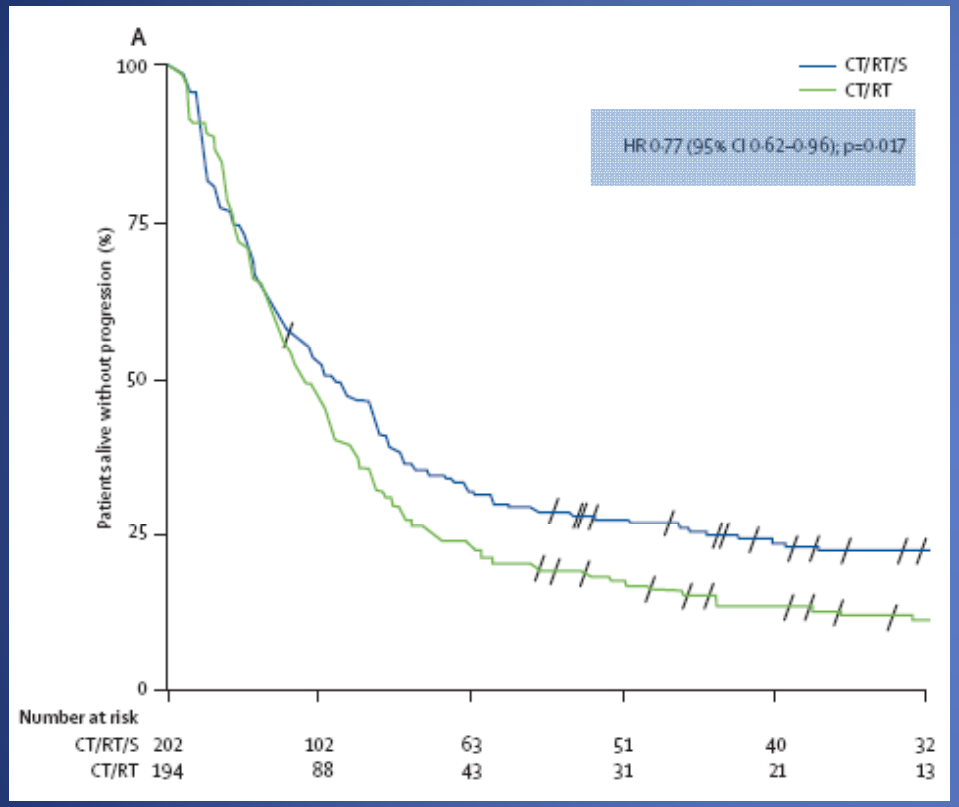
Trimodality is not optimal when a pneumonectomy is needed, due to a high mortality rate (14/15)

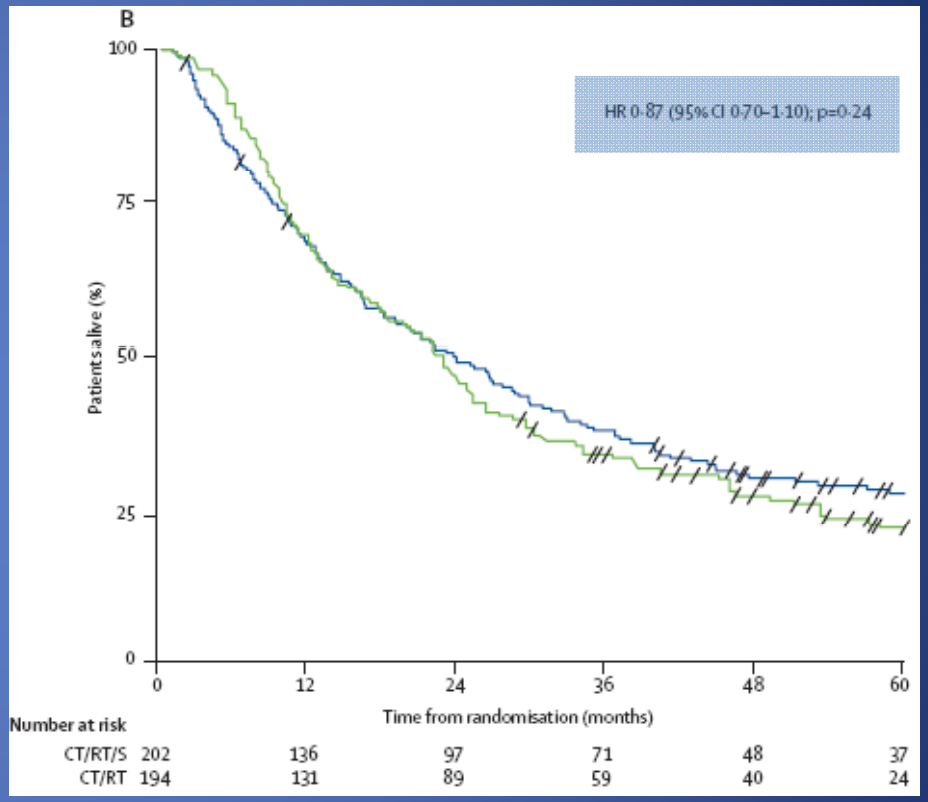
Surgery an experimental, but promising therapeutic option after chemoradiation in patients with stage IIINSCLC without mediastinal lymph node metastases at restaging and who can be resected by a radical lobectomy

GRADE 1 B : ACCP .CHEST 2007

Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

Lancet 2009; 374: 379–86





OS did not signifi cantly improved, even though PFS did, in patients who underwent trimodality treatment

OS improved for patients who underwent lobectomy, but not pneumonectomy, versus chemotherapy plus radiotherapy

Conclusion :Chemotherapy plus radiotherapy with or without resection (preferably lobectomy) are options for patients with stage IIIA(N2) non-small-cell lung cancer

Advanced Stage Non–Small Cell Lung Cancer

- Diagnosis of advanced nonsmall cell lung cancer greeted with considerable therapeutic nihilism despite significant advances in management of this disease over last decade
- Standard therapy for patients with advanced-stage disease is platinum-based double-agent chemotherapy
- Recent trials have investigated the addition of ‘‘targeted agent’’ in combination with platinum-based chemotherapy

What benefits can patients expect from chemotherapy ?

- Randomised trials have shown benefits in terms of palliation, improvement of survival, symptom control, quality of life and cost

Clinical Lung Cancer, 2009

Table 1 Select Clinical Trials and Meta-analyses Comparing Chemotherapy with Best Supportive Care[3-9]

Study (Year)	N	Treatment	ORR, %	Median Survival	1-Year Survival, %
Rapp et al (1988)[4]	53	Best supportive care	0	17 Weeks	10
	98	Vindesine + cisplatin	25.3	32.6 Weeks	22
	100	Cyclophosphamide + doxorubicin + cisplatin	15.3	24.7 Weeks	21
Cullen et al (1999)[5]	175	Best supportive care	0	4.8 Months	17
	176	Mitomycin + ifosfamide + cisplatin	32	6.7 Months	25
Cellerino et al (1991)[6]	61	Best supportive care	0	4.9 Months	23
	62	Cyclophosphamide + epirubicin + cisplatin alternated with methotrexate + etoposide + lomustine	21	8 Months (P = NS)	32
Cartei et al (1993)[7]	50	Best supportive care	NR	4 Months	12
	52	Cisplatin + mitomycin + cyclophosphamide	NR	8.5 Months	38.5
Spiro et al (2004)[8]	361	Best supportive care	0	5.7 Months	20
	364	One of 4 cisplatin-based regimens	25	8 Months	29
Shanafelt et al, Meta-analysis (2004)[9]	25 Trials	Best supportive care	0	5 Months	18
		Chemotherapy	7-42	7 Months	27
Non–Small Cell Lung Cancer Collaborative Group Meta-analysis (1995)[3]	52 Trials	Best supportive care	NR	6 Months	16
		Chemotherapy	NR	8 Months	26

What are the active chemotherapeutic drugs for which efficacy has been shown?

- Inactive (also called first-generation)
- Old (second-generation)
  - cisplatin, ifosfamide, mitomycin C, vindesine and vinblastine
- New (or modern or third-generation) drug
  - gemcitabine,paclitaxel, docetaxel and vinorelbine
- Targeted drugs
- ? Cancer vaccine

FIRST LINE THERAPY : HOW MANY & WHICH ?

TABLE Meta-analyses assessing the number of drugs needed in chemotherapy regimens

	Methodology	Outcome criteria	Trials n	Patients n	Result
Single agent *versus* polychemotherapy					
MARINO Lung Cancer 1995	MASRL	Mortality risk	9	1493	s
LILENBAUM Cancer 1998	IMA	Survival at 6 and 12 months	25	5156	s
One *versus* two drugs					
DELBALDO JAMA 2004	IMA	Median survival	30	6022	s
Two *versus* three drugs					
DELBALDO JAMA 2004	IMA	Median survival	30	4550	NS

MASRL: meta-analysis with systematic review of the literature; s: significant; IMA: isolated meta-analysis of the literature; NS: nonsignificant.

TABLE Guidelines for the management of advanced nonsmall cell lung cancer

Society	First-line therapy
Fédération Nationale des Centres de Lutte Contre le Cancer	Cisplatin-containing chemotherapy (performance status 0-1)
American Society of Clinical Oncology	Two-drug combination regimen (nonplatinum containing chemotherapy may be used as an alternatives to platinum-based regimen). Poor performance status: single-agent chemotherapy.
Cancer Care Ontario Program	Cisplatin-based chemotherapy
European Lung Cancer Working Party	Cisplatin-based chemotherapy with one of the regimens shown to be effective (single agent chemotherapy with a drug shown to be effective, may be considered in patients with poor performance status)
American College of Chest Physicians	Platinum-based chemotherapy with a new single agent (Eastern Cooperative Oncology Group performance status 0-1)

Eur Respir J 2009; 33: 915–930

CISPLATIN VS CARBOPLATIN

Table 3. Response rate in the nine trials included in the meta-analysis*

Trial (reference)	No. of patients (regimen)	Objective response (%)	OR (95% CI)	P†
Klastersky, 1990 (25)	114 (P-E)	24	1.87 (0.97 to 3.63)	.063
	114 (C-E)	14		
Jelic, 2001 (26)	112 (P-M-Vd)	37	1.09 (0.63 to 1.90)	.761
	104 (C-M-Vd)	35		
Bisset, 2001 (27)	20 (P-TPZ)	25	1.95 (0.42 to 8.95)	.393
	21 (C-TPZ)	14		
Rosell, 2002 (28)	309 (P-T)	27	1.09 (0.76 to 1.56)	.646
	309 (C-T)	25		
Schiller, 2002 (29)	303 (P-T)	21	1.40 (0.93 to 2.11)	.110
	299 (C-T)	16		
Zatloukal, 2003 (30)	87 (P-G)	41	1.70 (0.92 to 3.15)	.092
	89 (C-G)	29		
Fossella, 2003 (31)	408 (P-D)	32	1.47 (1.08 to 2.00)	.014
	406 (C-D)	24		
Mazzanti, 2003 (32)	62 (P-G)	42	1.59 (0.76 to 3.34)	.218
	58 (C-G)	31		
Paccagnella, 2004 (33)	74 (P-M-Vb)	42	1.31 (0.68 to 2.51)	.414
	79 (C-M-Vb)	35		
Total	1489 (P)	30	1.37 (1.16 to 1.61)	<.001
	1479 (C)	24		

* OR = odds ratio for nonresponse in patients treated with carboplatin versus those treated with cisplatin; CI = confidence interval; P = cisplatin; E = etoposide; C = carboplatin; M = mitomycin; Vd = vindesine; TPZ = tirapazamine; T = paclitaxel; G = gemcitabine; D = docetaxel; Vb = vinblastine.

† Two-sided *P* values were calculated using Pearson chi-square test and *U* test.

Cisplatin-based chemotherapy slightly superior to carboplatin-based chemotherapy in terms of response rate and, in certain subgroups, in prolonging survival without being associated with an increase in severe toxic effects

CISCA (CISplatin versus CArboplatin) Metaanalysis Group. J Natl Cancer Inst 2007

Non Platinum Vs Platinum

TABLE 3. Randomized Trials of Non-Platinum Versus Platinum-Based Doublet Chemotherapy Regimens in the First Line Treatment of NSCLC

Study	Trial Design	Treatment	No. Patients (n)	RR (%)	Median TTP (mo)	Median OS (mo)	1-yr Survival (%)	HR	P*
GOCG (Georgoulias, 2001)[29]	Primary endpoint: RR, TTP	Gemcitabine + docetaxel	222	30.2	4.6	9.5	30.6	NR	0.770 [docetaxel + gemcitabine vs. cisplatin + docetaxel]
	Superiority design	Cisplatin + docetaxel	219	32.4	8.0	10.0	42.0		
HECOG (Kosmidis, 2002)[31]	Primary endpoint: OS	Gemcitabine + paclitaxel	257	25.9	6.1	9.5	41.1	NR	0.32
	Superiority design	Carboplatin + paclitaxel	252	28.0	6.3	10.4	41.7		
Italo-Canadian study GEMVIN (Gridelli, 2003)[30]	Primary endpoint: QoL	Gemcitabine + vinorelbine	251	25	4.2	7.5	31.0	NR	0.94
	GemVin vs combined platinum regimens	Cisplatin + gemcitabine	125	(20)	(5.4)	(8.9)	(37.0)		
	2:1:1 randomization	Cisplatin + vinorelbine	125						
	Superiority design								
EORTC 08975 (Smit, 2003)[34]	Primary endpoint: OS	Paclitaxel + gemcitabine	133	33.3	5.6†	8.7	36.7	NR	0.660 [cisplatin + gemcitabine vs. cisplatin + paclitaxel]
	Patients' comparison to cisplatin + paclitaxel	Cisplatin + gemcitabine	168	36.9	5.1†	9.8	33.1		
	Superiority design	Cisplatin + paclitaxel	150	31.3	4.7†	9.1	35.9		0.388 [paclitaxel + gemcitabine vs. cisplatin + paclitaxel]
Georgoulias, 2004[35]	Primary endpoint: OS	Vinorelbine + paclitaxel	175	42.9	6.0	10.6	37.9	NR	0.9545
	Superiority design	Carboplatin + paclitaxel	185	46.0	7.0	11.0	42.7		
HORG (Georgoulias, 2005)[29]	Primary endpoint: OS	Gemcitabine + docetaxel	206	30.6	4.6	9.6	34.3	NR	0.965
	Superiority design	Cisplatin + vinorelbine	204	39.2	5.0	9.7	40.8		
France (Pujol, 2005)[33]	Primary endpoint: PFS	Gemcitabine + docetaxel	155	31.6	4.2	11.1	46.0	NR	0.65 [0.45 – 0.95]
	Superiority design	Cisplatin + vinorelbine	156	35.9	4.0	9.6	42.0		
Alpha Oncology Trial (A1-000021) (Treat, 2005)[36]	Primary endpoint: OS	Gemcitabine + paclitaxel	326	28.2	3.9	9.5	35.0	NR	0.8156 [carboplatin + gemcitabine vs. carboplatin + paclitaxel]
	Patients' comparison to carboplatin + paclitaxel	Carboplatin + gemcitabine	326	21.7	5.2	7.6	22.1		
	Superiority design	Carboplatin + paclitaxel	328	36.3	5.0	7.9	33.0		0.9196 [gemcitabine + paclitaxel vs. carboplatin + paclitaxel]
HECOG (Kosmidis, 2008)[32]	Primary endpoint: OS	Paclitaxel + gemcitabine	224	31.0	5.03	10.6	42.0	NR	0.41
	Superiority design	Carboplatin + gemcitabine	227	27.0	5.11	10.5	42.0		
D0112 (Riggs, 2008)[37]	Primary endpoint: OS	gemcitabine + docetaxel	466	NR	4.0†	7.9	33.6	1.02	0.736
	Non-inferiority design	Carboplatin + docetaxel	464	NR	3.9†	7.9	35.0		

EORTC indicates European Oncology Research and Treatment; GOCG, Greek Oncology Cooperative Group; HECOG, Hellenic Cooperative Oncology Group; HORG, Hellenic Oncology Research Group; HR, hazard ratio; NR, not reported; OS, overall survival; TTP, time to tumor progression.

*P value are for the primary endpoint.

†Progression free survival.

None of the clinical trials have been able to show statistically significant survival benefit when compared with platinum-based regimens

Clin Pulm Med 2009;16: 157–171

OPTIMAL DURATION

TABLE 1. Select Phase III Trials Investigating the Duration of Platinum-Based Therapy

First Author	Year	Chemotherapy	Treatment arms (*n*)	Time to disease progression	Median survival time	1-yr Survival
Smith[13]	2001	MVP	3 cycles (155)	5 mo	6 mo	22%
			6 cycles (153)	5 mo	7 mo	25%
Socinski[12]	2002	CP	4 cycles (114)	NR	6.6 mo	28%
			Continuation (116)[a]	NR	8.5 mo	34%
Von Plessen[16]	2006	CV	3 cycles (150)	16 wk	28 wk	25%
			6 cycles (147)	21 wk	32 wk	25%
Park[14]	2007	Cisplatin-based	4 cycles (156)[b]	4.6 mo[c]	15.9 mo	59%
			6 cycles (158)	6.2 mo	14.9 mo	62.4%
Barata[15]	2007	CG	4 cycles (110)	4 mo	7 mo[c]	NR
			6 cycles (110)	5 mo	12 mo	NR

[a] Patients continued therapy until disease progression or unacceptable toxicity.
[b] Patients who had stable disease or response after cisplatin in combination with paclitaxel, docetaxel or gemcitabine were randomized to two or four additional cycles of therapy. Numbers reflect patients randomized.
[c] *Statistically significant difference in the two treatment arms.*
MVP, mitomycin, vinblastine, cisplatin; CP, carboplatin/paclitaxel; CG, carboplatin/gemcitabine; CV, carboplatin/vinorelbine; NR, not reported.

J Thorac Oncol. 2009;4: 243–250

Use of more than 4 cycles of first-line chemotherapy with third-generation regimens significantly increases progression-free survival but not overall survival and associated with higher incidence of adverse events. There is no evidence to support continuous chemotherapy until progression in patients with lung cancer

EUROPEAN JOURNAL OF CANCER 4 5 (2 0 0 9) 6 0 1 –6 0 7

Table 1: Selected First-Line Chemotherapy Trials in Patients with Advanced Non–Small-Cell Lung Cancer with PS 2

Study	Phase	No. of Patients with PS 2 (Total)	Drug Regimen	RR, %	Survival
Lilenbaum[10] CALGB 9730 (Prospective Subset Analysis)	III	99 PS 2 (284)	**Carboplatin** AUC 6 + **Paclitaxel**	24	MS, 4.7 months 1-year OS, 18%
			vs.		
			Paclitaxel	10	MS, 2.4 months 1 year OS, 10%
Langer[12] STELLAR-3	III	400	**Carboplatin** AUC 6 + **Paclitaxel** 225 mg/m² Q3	36	MS, 5.8 months 1-year OS, 19%
			vs.		
			Carboplatin AUC 6 + **PPX** 210 mg/m² Q3	21	MS, 7.2 months 1-year OS, 28%
O'Brien[13] STELLAR-4	III	378	**PPX** 175 mg/m² Q3	11	MS, 7.3 months 1-year OS, 26%
			vs.		
			Gemcitabine 1000 mg/m² d 1, 8, 15 Q4 or **Vinorelbine** 30 mg/m² d 1, 8, 15 Q4	15	MS, 6.6 months 1-year OS, 28%
Obasaju[11] US Oncology	III	161	**Gemcitabine** 1250 mg/m² d 1, 8 Q3W	12	MS, 5.2 months 1-year OS, 24%
			vs.		
			Gemcitabine 1000 mg/m² d 1, 8 + **Carboplatin** AUC 5 d 1 Q3W	36	MS, 6.9 months 1-year OS, 31%

Abbreviations: MS = median survival; OS = overall survival; PPX = paclitaxel poliglumex; PS = performance status; RR = response rate

[a] N-values represent number of patients randomized.
[b] The hazard ratio of progression-free survival was 0.77 (95% CI, 0.56–1.07; $p = 0.65$), and the hazard ratio for overall survival was 1.08 (95% CI, 0.79–1.47; $p = 0.65$).
[c] Data reported as time after randomization and for time to tumor progression p value <0.001, and for overall survival p value = 0.172.

What is the definition of “targeted therapy”

- Form of treatment designed to specifically inhibit molecules that provide advantageous growth signals to cancer cells
- EGFR Inhibitors
  - Gefitinib (Iressa)
  - Erlotinib (Tarceva)
- EGFR Monoclonal antibodies
  - Cetuximab (Erbitux)
- VEGF Monoclonal antibodies
  - Bevacizumab (Avastin)

TARGETED THERAPY AS FIRST LINE

TABLE 4. Negative Randomized Trials of Chemotherapy With Targeted Agents in the First Line Treatment of Advanced NSCLC

Study	Agent	Treatment	No. Patients (n)	RR (%)	Median PFS (mos)	Median OS (mos)	1 yr Survival (%)	HR (95% CI)	*P*
(Smylie, 2001)[47]	Prinomastat	Carboplatin + paclitaxel + prinomastat 15 mg bid	198	18	4.3	9.1	40	NR, NS	NR, NS
		Carboplatin + paclitaxel + prinomastat 10 mg bid	197	19	3.3	8.6	35		
		Carboplatin + paclitaxel + prinomastat 5 mg bid	84	27	3.6	9.3	30		
		Carboplatin + paclitaxel + placebo	198	21	3.5	10.2	29		
(Bissett, 2005)[48]	Prinomastat	Cisplatin + gemcitabine + prinomastat 15 mg bid	181	27	6.1	11.5	43	NR	0.82
		Cisplatin + gemcitabine + placebo	181	26	5.5	10.8	38		
BR.18 (Leighl, 2005)[46]	BMS-275291	Carboplatin + paclitaxel + BMS-27591 1200 mg qd	387	25.8	4.9	8.6	NR	1.09 (0.93–1.28)	0.30
		Carboplatin + paclitaxel + placebo	387	33.7	5.3	9.2	NR		
Combination with protein kinase C-alpha subunit antisense oligonucleotide									
(Lynch, 2003)[45]	Aprinocarsen (LY900003, Affinitak)	Carboplatin + paclitaxel + aprinocarsen 2 mg/kg/d CIV days 1 14	308	37	4.7*	9.7	41	NR	0.8054
		Carboplatin + paclitaxel	307	36	4.5*	10.0	42		
(Paz-Ares, 2006)[44]	Aprinocarsen (LY900003, Affinitak)	Cisplatin + gemcitabine + aprinocarsen 2 mg/kg/d CIV days 1–14	342	28.9	5.0	10.0	41.8	1.05 (0.88–1.25)	0.613
		Cisplatin + gemcitabine	328	35.0	5.2	10.4	44.9		
Combination with farnesyl protein transferase inhibitor									
(Blumenschein, 2005)[43]	Lonafarnib (SCH66336)	Carboplatin + paclitaxel + lonafarnib 100 mg bid	308	NR	4.6	4.8	NR	NR	0.3869
		Carboplatin + paclitaxel + placebo 100 mg bid	308	NR	5.1	5.6	NR		
Combination with retinoid-X receptor (RXR) agonist									
SPIRIT I (Ramlau, 2008)[41]	Bexarotene	Cisplatin + vinorelbine + bexatrotene 400 mg/m^2/d	311	16.7	4.3	8.7	13.2*	NR	0.3
		Cisplatin + vinorelbine	312	24.4	5.0	9.9	15.7*		
SPIRIT II (Blumenschein, 2008)[42]	Bexarotene	Carboplatin + paclitaxel + bexatrotene 400 mg/m^2/d	306	19.3	4.1	8.5	12.4*	NR	0.2
		Carboplatin + paclitaxel	306	23.5	4.9	9.1	16.3*		
Combination with immune booster (Toll-like receptors 9 agonist)									
(Hirsh, 2008)[39]	PF-3512676	Carboplatin + paclitaxel + PF-3512676, then PF-3512676 maintenance	408	25	4.8	10.2	42	1.06 (0.89–1.26)	0.53
		Carboplatin + paclitaxel	420	23	4.8	10.3	44		
(Manegold, 2008)[40]	PF-3512676	Cisplatin + gemcitabine + PF-3512676, then PF-3512676 maintenance	416	27	5.1	11.1	47	0.98 (0.83–1.16)	0.84
		Cisplatin + gemcitabine	423	29	5.2	10.7	46		
Combination with hypoxic cells cytotoxin									
SWOG0003 (Williamson, 2005)[38]	Tirapazamine	Carboplatin + paclitaxel + tirapazamine 260 mg/m^2	181	26	5	9	NR	NR	0.35
		Carboplatin + paclitaxel	186	35	5	9	NR		

SPIRIT indicates studies providing investigational research in targretin; HR, hazard ratio; OS, overall survival; PFS, progression free survival.
*2-yr survival.

Clin Pulm Med 2009;16: 157–171

VEGF & EGFR: LIGHT AT THE END OF TUNNEL

TABLE 5. Randomized Trials of Chemotherapy With Targeted Agents Against EGFR and VEGF in the First Line Treatment of NSCLC

Study	Primary Endpoint	Treatment	No. Patients (n)	RR (%)	Median PFS (mos)	Median OS (mos)	1 yr Survival (%)	HR (95% CI)	$p^{\S}$
Combination with EGFR inhibitors									
TALENT (Gatzemeier, 2007)[54]	OS; Superiority design	Cisplatin + gemcitabine + erlotinib 150 mg/d × 6 cycles, then erlotinib until progression	586	31.5	5.5	10.0	41	1.06 (0.90–1.23)	0.49
		Cisplatin + gemcitabine + placebo × 6 cycles, then placebo until progression	586	29.9	5.7	10.3	42		
TRIBUTE (Herbst, 2005)[55]	OS; Superiority design	Carboplatin + paclitaxel + erlotinib 150 mg/d × 6 cycles, then erlotinib until progression	539	21.5	5.1	10.6	NR	0.995 (086–1.16)	0.95
		Carboplatin + paclitaxel + placebo × 6 cycles, then placebo until progression	540	19.3	4.9	10.5	NR		
INTACT-1 (Giaccone, 2004)[52]	OS; Superiority design	Cisplatin + gemcitabine + gefitinib 500 mg/d, then gefitinib until progression	365	50.3	5.5*	9.9	43	NR	0.4560
		Cisplatin + gemcitabine + gefitinib 250 mg/d, then gefitinib until progression	365	51.2	5.8*	9.9	41		
		Cisplatin + gemcitabine + placebo, then placebo until progression	363	47.2	6.0*	10.9	44		
INTACT-2 (Herbst, 2004)[53]	OS; Superiority design	Carboplatin + paclitaxel + gefitinib 500 mg/d, then gefitinib until progression	347	30.0	4.6*	8.7	37	NR	0.6385
		Carboplatin + paclitaxel + gefitinib 250 mg/d, then gefitinib until progression	345	30.4	5.3*	9.8	41		
		Carboplatin + paclitaxel + placebo, then placebo until progression	345	28.7	5.0*	9.9	42		
BMS-099 (Lynch, 2007)[57]	PFS	Carboplatin + taxanes + cetuximab	338	25.7	4.4	NR	NR	0.902 (0.761–1.069)	0.2358
		Carboplatin + taxanes	338	17.2	4.24	NR	NR		
FLEX (Pirker, 2008)[51]	OS; Superiority design	Cisplatin + vinorelbine + cetuximab, then cetuximab maintenance	557	36	4.8	11.3	47	0.871 (0.762–0.996)	0.0044
		Cisplatin + vinorelbine	568	29	4.8	10.1	42		
Combination with anti-angiogenesis inhibitors									
E4599 (Sandler, 2006)[49]	OS; Superiority design	Carboplatin + paclitaxel + bevacizumab 15 mg/kg, then bevacizumab 15 mg/kg maintenance	444	35	6.2	12.3	51	0.79 (0.67 0.92)	0.003
		Carboplatin + paclitaxel	434	15	4.5	10.3	44		
AVAIL (Manegold, 2007)[50]	PFS; Superiority design	Cisplatin + gemcitabine + bevacizumab 15 mg/kg, then bevacizumab 15 mg/kg maintenance	351	30	6.5	NR	NR	0.82† (0.68–0.98) 0.75‡ (0.62–0.91)	0.0301† 0.0026‡
		Cisplatin + gemcitabine + bevacizumab 7.5 mg/kg, then bevacizumab 7.5 mg/kg maintenance	345	34	6.7	NR	NR		
		Cisplatin + gemcitabine + placebo	347	20	6.1	NR	NR		
ESCAPE (Scagliotti, 2008)[56]	OS; Superiority design	Carboplatin + paclitaxel + sorafenib	464	30	NR	10.7	NR	1.16 (0.95–1.43)	0.93
		Carboplatin + paclitaxel + placebo	462	24	NR	10.6	NR		

AVAIL indicates Avastin in lung cancer; ECOG, Eastern Cooperative Oncology Group; ESCAPE, evaluation of sorafenib, carboplatin, paclitaxel efficacy; FLEX, First-Line treatment for patients with EGFR-expressing advanced NSCLC; HR, hazard ratio (HR is reported for primary endpoint of the trial; INTACT, Iressa NSCLC Trial assessing combination treatment; TALENT, Tarceva Lung Cancer Investigation; TRIBUTE, Tarceva Response in Conjugation with Paclitaxel and Carboplatin; CI, confidence interval; HR, hazard ratio; NR, not reported; NS, not significant; OS, overall survival; PFS, progression-free survival; RR, response rate; q3w, every 3 wk. HR and *P* value reported for median OS. Pairwise comparison of the 2 platinum-docetaxel arms to cisplatin-vinorelbine is listed separately.

*Time to progression.

†Comparison between 15 mg/kg of bevacizumab and placebo.

‡Comparison between 7.5 mg/kg of bevacizumab and placebo.

§*P* value for primary endpoint (RR).

Clin Pulm Med 2009;16: 157–171

The importance of EGFR as a target

EGFR over expression observed in 13% to 80%of NSCLC
Associated with poorer outcome

Clinical Lung Cancer(9) S109-15, 2008

EGFR – TARGETED THERAPIES

Table Selected Epidermal Growth Factor Receptor–Directed Drugs in Non–Small-Cell Lung Cancer

Class of Drugs	Clinical Status
Tyrosine Kinase Inhibitors	
Erlotinib	Approved (second- and third-line)
Gefitinib	Approved in certain countries
Monoclonal Antibodies	
Cetuximab	Phase III
Matuzumab	Phase II
Panitumumab	Phase II
Dual and Multikinase Inhibitors	
Vandetanib	Phase III
Lapatinib	Phase II
Canertinib	Phase II

Clin Pulm Med 2009;16: 157–71

TABLE 5. Randomized Trials of Chemotherapy With Targeted Agents Against EGFR and VEGF in the First Line Treatment of NSCLC

Study	Primary Endpoint	Treatment	No. Patients (n)	RR (%)	Median PFS (mos)	Median OS (mos)	1 yr Survival (%)	HR (95% CI)	P§
Combination with EGFR inhibitors									
TALENT (Gatzemeier, 2007)[54]	OS; Superiority design	Cisplatin + gemcitabine + erlotinib 150 mg/d × 6 cycles, then erlotinib until progression	586	31.5	5.5	10.0	41	1.06 (0.90–1.23)	0.49
		Cisplatin + gemcitabine + placebo × 6 cycles, then placebo until progression	586	29.9	5.7	10.3	42		
TRIBUTE (Herbst, 2005)[55]	OS; Superiority design	Carboplatin + paclitaxel + erlotinib 150 mg/d × 6 cycles, then erlotinib until progression	539	21.5	5.1	10.6	NR	0.995 (086–1.16)	0.95
		Carboplatin + paclitaxel + placebo × 6 cycles, then placebo until progression	540	19.3	4.9	10.5	NR		
INTACT-1 (Giaccone, 2004)[52]	OS; Superiority design	Cisplatin + gemcitabine + gefitinib 500 mg/d, then gefitinib until progression	365	50.3	5.5*	9.9	43	NR	0.4560
		Cisplatin + gemcitabine + gefitinib 250 mg/d, then gefitinib until progression	365	51.2	5.8*	9.9	41		
		Cisplatin + gemcitabine + placebo, then placebo until progression	363	47.2	6.0*	10.9	44		
INTACT-2 (Herbst, 2004)[53]	OS; Superiority design	Carboplatin + paclitaxel + gefitinib 500 mg/d, then gefitinib until progression	347	30.0	4.6*	8.7	37	NR	0.6385
		Carboplatin + paclitaxel + gefitinib 250 mg/d, then gefitinib until progression	345	30.4	5.3*	9.8	41		

BEVACIZUMAB

- Bevacizumab: recombinant, humanized, monoclonal, anti-VEGF antibody, blocks binding of human VEGF to its receptors

Critera for treatment

- Non- squamous NSCLC
- No untreated CNS mets
- No history of hemoptysis

Oncologist 2007;12;713-718

ONGOING TRIALS WITH BEVACIZUMAB

Table 1 Trials of NSCLC Allowing in Patients with Brain Metastases to Be Enrolled

Trial	Phase	Supporter
Bevacizumab in Combination with Pemetrexed as Second Line Therapy in Patients with Stable Brain Metastases from NSCLC (Excluding Squamous Cell)	II	Stanford University
Bevacizumab in Combination with First- or Second-Line Therapy in Subjects with Brain Metastases due to Non-Squamous NSCLC (PASSPORT)	II	Genentech
Study Comparing Bevacizumab Therapy with or Without Erlotinib for First-Line Treatment of NSCLC (ATLAS)	III	Genentech

Table 2 Trials of Bevacizumab Allowing Squamous Cell Histology

Trial	Phase	Supporter
Bevacizumab in Combination with Platinum-Based Chemotherapy in Patients with Advanced or Recurrent Squamous NSCLC	II	Hoffman La-Roche
Bevacizumab plus Carboplatin and Paclitaxel in Subjects with Advanced, Previously Untreated, Squamous NSCLC (SIERRA)	II	Genentech
Bevacizumab plus Carboplatin and Paclitaxel in Subjects with Advanced, Previously Untreated, Squamous NSCLC (BRIDGE)	II	Genentech

Table Bevacizumab with Chemotherapy as Adjuvant or Neoadjuvant Treatment of Resectable NSCLC

Title	Phase	Supporter
Neoadjuvant Therapy with Docetaxel, Carboplatin, and Bevacizumab in Patients with Resectable Early-Stage NSCLC	II	University of California San Francisco Helen Diller Family Comprehensive Cancer Center
Neoadjuvant Bevacizumab in Combination with Paclitaxel and Carboplatin in Surgically Resectable NSCLC	II	University of Chicago
Randomized Trial of Adjuvant Chemotherapy with or Without Bevacizumab for Patients with Completely Resected Stage IB-IIIA NSCLC	III	ECOG

Clinical Lung Cancer 2008

GEFITINIB MONOTHERAPY

Pooled analysis of the prospective trials of gefitinib monotherapy for EGFR-mutant non-small cell lung cancers

Results—A total of 101 patients were pooled from these studies. 59 received gefitinib as their first line of therapy and 42 after having received chemotherapy. The combined rate of complete and partial response (CR+PR) in the 99 measured patients was 80.8% (80/99) and only 7.1% (7/99) had progressive disease as best response. The response rate (CR+PR) for exon 19 deletion and L858R patients were 80.3% (53/66) and 81.8% (27/33), respectively. The median progression-free survival ranged from 7.7 to 12.9 months. Overall survival had not been reached in 4/5 reports and was 15.4 months in one of them. Gefitinib administration was safe (<50% of patients developed grade 1-2 skin rash or diarrhea) and interstitial lung disease was only reported in 2 patients (2%), without deaths.

Conclusions—Gefitinib monotherapy leads to objective responses in most patients with EGFR mutations. Both L858R and deletion 19 mutations derived similar clinical benefits. Small molecule TKIs are the new treatment paradigm for EGFR-mutant NSCLC.

Lung Cancer. 2007

Table 2: Selected Trials of First-Line Targeted Therapy in Patients with Advanced Non–Small-Cell Lung Cancer with PS 2

Study	No. of Patients with PS 2 (Total)	Drug Regimen	RR (SD), %	Toxicity	Survival, Months
Hesketh[21] S0341	72	**Erlotinib** 150 mg/day	8 (35)	Grade 3/4: Fatigue, 17% Rash, 10% Diarrhea, 7%	MS, 5 PFS, 2.1
Lilenbaum[22] (Randomized)	103	**Erlotinib** 150 mg/day	4 (37)	Grade 3/4: 25% (rash, diarrhea)	MS, 6.6 PFS, 1.9
		vs.			
		Carboplatin AUC 6 + **Paclitaxel** 200 mg/m^2 every 3 weeks	12 (43)	Grade 3/4: 37% (emesis, alopecia, neuropathy, fatigue)	MS, 9.7 PFS, 3.5
Goss[23] INSTEP (Randomized)	201	**Gefitinib** 250 mg/day	6	Rash: 40% vs. 11% Diarrhea: 51% vs. 20% Fatigue: 15% vs. 22%	PFS HR, 0.821 (P = .21)
		vs.			
		Placebo	1		
Morere[24] IFCT-0301 (Randomized)	127 (PS 2/3)	**Gefitinib** 250 mg/day	20.9 (PR & SD)	Grade 4 toxicity: 4%	MS, 2.2 PFS, 1.9
		vs.			
		Gemcitabine 1250 mg/m^2 days 1, 8 every 3 weeks	33.4 (PR & SD)	14%	MS, 2.4 PFS, 2.1
		vs.			
		Docetaxel 75 mg/m^2 every 3 weeks	38.1 (PR & SD)	11%	MS, 3.5 PFS, 2
Lilenbaum[26] CALGB 30402 (Randomized)	55	**Docetaxel** 30 mg/m^2 days 1, 8, 15 every 4 weeks + **Cetuximab** 400 mg/m^2 every week	10.5	Hematologic: 17% (docetaxel + cetuximab) vs. 17% (docetaxel + bortezomib)	MS, 3.8 PFS, 3.1
		vs.			
		Docetaxel 30 mg/m^2 days 1, 8, 15 every 4 weeks + **Bortezomib** days 1, 8, 15 every 4 weeks	13.6	Nonhematologic: 44% (docetaxel + cetuximab) vs. 36% (docetaxel + bortezomib)	MS, 3.3 PFS, 1.8
Gridelli[25] CALC1-PS2 (Randomized)	42	**Gemcitabine** 1200 mg/m^2 days 1, 8 every 3 weeks + **Cetuximab** 250 mg/m^2 every week	9.1 (50)	Grade 3/4: Rash: 32% vs. 5% Fatigue: 9% vs. 5% Heme: 3% vs. 20%	MS, 10.3 PFS, 5.75
		vs.			
		Gemcitabine 1200 mg/m^2 days 1, 8 every 3 weeks → **Cetuximab** 250 mg/m^2 every week (60% of patients not able to start cetuximab in sequential arm)	10 (15)		MS, 6.5 PFS, 2.25

Abbreviations: MS = median survival, PFS = progression-free survival; PR = partial response; PS = performance status; SD = stable disease

SECOND LINE TREATMENT OF METASTATIC NSCLC

- Most stage IIIB/IV patients experience disease progression after 1 st line chemo and,50–60% of fit enough to receive second-line treatment
- Patients with a good PS, non-squamous histology and female gender likely to receive second-line therapy

Proc Am Thorac Soc Vol 6. 2009

- Currently, only 3 drugs approved by FDA for second line treatment of NSCLC: docetaxel, pemetrexed, and erlotinib
- Erlotinib, only third-line option in recurrent NSCLC

Eur Respir J 2009; 33: 915–930

RCT OF SECOND LINE CHEMO

TABLE 8. Selected Randomized Phase III Trials for Second Line Treatment of NSCLC

Study	Primary Endpoint and Trial Design	Treatment	No. Patients (n)	RR (%)	Median PFS (mos)	Median OS (mos)	1-yr Survival (%)	HR (95% CI)	*P*
TAX 317 (Shepherd, 2000)[68]	Primary endpoint: OS Superiority design	Docetaxel 75 mg/m² or 100 mg/m² q3w	103	5.8	2.5*	7.0	29	NR	0.047
		Best supportive care	100	—	1.6*	4.6	19		
TAX 320 (Fossella, 2000)[67]	Primary endpoint: OS Superiority design	Docetaxel 100 mg/m² (D100)	125	10.8	2.0*	5.5	21	NR	NS (D100 vs. V/I) 0.025 (D75 vs. V/I)
		Docetaxel 75 mg/m² (D75)	125	6.7	2.0*	5.7	32		
		Ifosfamide OR vinorelbine (V/I)	123	0.8	1.8*	5.6	19		
JMEI (Hanna, 2004)[69]	Primary endpoint: OS	Docetaxel 75 mg/m² q3w	288	8.8	2.9	7.9	29.7	0.99 (0.80–1.20)	0.226
	Superiority and noninferiority design	Pemetrexed 500 mg/m² q3w	283	9.1	2.9	8.3	29.7		
(Ramlau, 2006)[76]	Primary endpoint: 1-yr survival Noninferiority design	Docetaxel 75 mg/m² q3w	415	5	3.0*	7.2	28.7	NR	0.057
		Oral topotecan 2.3 mg/m² days 1–5 q3w	414	5	2.6*	6.5	25.1	NR	
(Krazkowski, 2007)[78]	Primary endpoint: PFS Noninferiority design	Docetaxel 75 mg/m² q3w	277	5.5	2.3	7.2	NR	1.004 (0.84–1.20)	0.965
		Vinflunine 320 mg/m² q3w	274	4.4	2.3	6.7	NR		
STELLA 2 (Paz-Ares, 2008)[77]	Primary endpoint: OS Superiority and noninferiority design	Docetaxel 75 mg/m² q3w	422	12	2.6†	6.9	29	1.09 (0.94–1.27)	0.26
		Paclitaxel poliglumex 210 mg/m² q3w (PS 0–75 mg/m² q3w (PS2)	427	8	2.0†	6.9	25		
EGFR inhibitors in 2nd line treatment of NSCLC									
NCIC BR.21 (Shepherd, 2005)[70]	Primary endpoint: OS Superiority design	Erlotinib 150 mg/d	488	8.9	2.2	6.7	31	0.70 (0.58–0.85)	<0.001
		Placebo	243	<1	1.8	4.7	22		
ISEL (Thatcher, 2005)[72]	Primary endpoint: OS Superiority design	Gefitinib 250 mg/d	1129	8.0	3.0‡	5.6	27	0.89 (0.77–1.02)	0.087
		Placebo (3% cross-over from placebo to gefitinib)	563	1.3	2.6†	5.1	21		
V 15-32 (Niho, 2007)[74]	Primary endpoint: OS Noninferiority design	Gefitinib 250 mg/d	245	22.5	2.0	11.5	48	1.01 (0.80–1.27)	0.914
		Docetaxel 60 mg/m² q3w	244	12.8	2.0	14.0	54		
INTEREST (Douillard, 2008)[75]	Primary endpoint: OS Noninferiority design	Gefitinib 250 mg daily	723	9.1	2.2	7.6	32	1.020 (0.91–1.15)	NR
		Docetaxel 75 mg/m² q3w	710	7.6	2.7	8.0	34		

INTEREST indicates Iressa NSCLC Trial evaluating response and survival against taxotere; ISEL, Iressa Survival Evaluation in Lung cancer; STELLAR, selected targeted efficacy in lung cancer to lower adverse reactions; CI, confidence interval; HR, hazard ratio (HR is reported for primary endpoint of the trial); NR, not reported; NS, not significant; OS, overall survival; PFS, progression-free survival; RR, response rate; q3w, every 3 wk.

*Time to treat failure (TTP).

†HR and *P* value reported for median OS.

‡Time to progression.

Clin Pulm Med 2009;16: 157–71

METAANALYSIS OF 2ND LINE CHEMO THERAPY REGIMEN

Second-Line Treatments in Non-small Cell Lung Cancer

Davide Tassinari, Emanuela Scarpi, Sergio Sartori, Emiliano Tamburini, Carlotta Santelmo, Paola Tombesi and Luigi Lazzari-Agli

Chest 2009;135;1596-1609; Prepublished online February 18, 2009; DOI 10.1378/chest.08-1503

Conclusion: **Second-line treatments in NSCLC seem to improve the main outcomes better than supportive care. Docetaxel administration every 3 weeks probably remains the "gold standard" because at present the data in literature are not enough to support a greater efficacy of other alternative options. Further trials are needed to identify a clinical and biological profile that could predict the response to treatments and a criterion to select the patients to be treated with chemotherapy or EGFR inhibitors.** ***(CHEST 2009; 135:1596–1609)***

Multitargeted Antifolates in NSCLC : Pemetrexed

- Pemetrexed approved for treatment of second-line NSCLC based on results from a randomized phase III study with a noninferiority statistical with docetaxel

J Clin Oncol 2004; 22:1589-97.

in 2008 granted approval for histologically based first-line treatment by both the EMEA and FDA

Clin Pulm Med 2009;16: 157–71

Table 1 Treatment-by-Histology Interactions for Overall Survival and Progression-Free Survival in the Cisplatin/Pemetrexed Versus Cisplatin/Gemcitabine Study

Efficacy Measure	Nonsquamous*		Squamous	
	Cis/Pem (n = 618)	Cis/Gem (n = 634)	Cis/Pem (n = 244)	Cis/Gem (n = 229)
Median OS, Months	11	10.1	9.4	10.8
HR (95% CI)	0.84 (0.74-0.96)		1.23 (1.00-1.51)	
Treatment-by-Histology Interaction Test	$P = .002$			
Median PFS, Months	5.3	5.00	4.4	5.5
HR (95% CI)	0.95 (0.84-1.06)		1.36 (1.12-1.65)	
Treatment-by-Histology Interaction Test	$P = .002$			

*Nonsquamous histology includes adenocarcinoma, large-cell, and not otherwise specified histologies.

Abbreviations: Cis = cisplatin; Gem = gemcitabine; HR = hazard ratio; OS = overall survival; Pem = pemetrexed; PFS = progression-free survival

SPECIAL POPULATIONS

TABLE 9. Recent Phase III Randomized Trials Results With Survival Data Specifically Analyzed for Never-Smokers

Study	Treatment Arm	No. Patients (n)	RR (%)	Median TTP (mo)	Median OS (mo)	1-yr Survival (%)	HR (95% CI)	*P*
1st line treatment								
TRIBUTE[55]	Carboplatin + paclitaxel + erlotinib 150 mg/d	72	30.0	6.0	22.5	NR	0.49 (0.28–0.85)	0.01
	Carboplatin + paclitaxel + placebo	44	11.0	4.3	10.1	NR		
TALENT[54]	Cisplatin + gemcitabine + erlotinib 150 mg/d	8	NR	7.9	NR*	NR	NR	0.02
	Cisplatin + gemcitabine	10	NR	5.4	11.4	NR		
(Scagliotti, 2008)[26]	Cisplatin + gemcitabine	122	NR	NR	15.3	NR	1.00	NR
	Cisplatin + pemetrexed	128	NR	NR	15.9	NR	(0.71–1.41)	
2nd line treatment								
BR.21[70,83]	Erlotinib 150 mg/d	104	24.7	NR	NR	NR	0.42	<0.001
	Placebo	42	NR	NR	NR	NR	(0.28–0.64)	
ISEL[82]	Gefitinib 250 mg/d	250	18.1	5.8†	8.9	NR	0.67	0.012
	Placebo	125	—	2.6†	6.1	NR	(0.49–0.92)	
INTEREST[75]	Gefitinib 250 mg/d	148	NR	NR	14.1	NR	0.93	0.623
	Docetaxel 75 mg/m2	143	NR	NR	13.9	NR	(0.70–1.23)	

INTEREST indicates Iressa NSCLC Trial evaulating response and survival against taxotere; ISEL, Iressa Survival Evaulation in Lung cancer; TALENT, Tarceva Lung Cancer Investigation; TRIBUTE, Tarceva Response in Conjugation with Paclitaxel and Carboplatin; NR, not reported; TTP, time to progression.

- Generally found in females, of adenocarcinoma histology, of Asian ethnicity, and has better survival outcome after curative surgery or chemotherapy for metastatic disease
- Neversmokers with NSCLC have a higher frequency of EGFR mutations and have higher responses to oral EGFR TKIs IPASS TRIAL

Clin Pulm Med 2009;16: 157–71

ELDERLY / PS 2 : TWO BETTER THAN ONE !

TABLE 11. Phase III Randomized Trials of First Line Treatment of Advanced NSCLC in Elderly Patients or PS2 Patients

Study	Trial Design	Treatment	No. Patients (n)	RR (%)	Median PFS (mo)	Median OS (mo)	1-yr Survival (%)	HR (95% CI)	P
Elderly patients: 1st line prospective treatment									
MILES (Gridelli, 2003)[87]	Primary endpoint: OS Single agent vs. GEMVIN Superiority design	Vinorelbine (V)	233	18	4.2 (18 wk)*	8.4 (36 wk)	38	1.17 [GEMVIN vs. V] (0.95–1.44)	0.93 (GEMVIN vs. V)
		Gemcitabine (G)	233	16	4.0 (17 wk)*	6.5 (28 wk)	28	1.06 [GEMVIN vs. G] (0.86–1.29)	0.69 (GEMVIN vs. G)
		Gemcitabine + vinorelbine (GEMVIN)	232	21	4.4 (19 wk)*	7.0 (30 wk)	30		
Elderly patients: retrospective subgroup analysis 1st line treatment									
CALGB 9730 (Lilenbaum, 2005)[88]		Carboplatin + paclitaxel	77	36	NR	8.0	35	0.84 (0.61–1.16)	0.289
		Paclitaxel alone	78	21	NR	5.8	31		
TAX326 (Belani, 2005)[89]	OS: superiority design	Cisplatin + docetaxel (DC)	149	NR	NR	12.6	52	1.34 (1.011–1.776) [VC vs. DC]	NR
		Carboplatin + docetaxel (DCb)	118	NR	NR	9.0	39	0.965 (0.714–1.305) [VC vs. DCb]	
		Cisplatin + vinorelbine (VC)	134	NR	NR	9.9	41		
ECOG 4599 (Ramalingam, 2008)[90]	OS: superiority design	Carboplatin + paclitaxel + bevacizumab	111	28.7	5.9	11.3	46	0.87 (0.64–1.19)	0.4
		Carboplatin + paclitaxel	113	17.3	4.9	12.1	50		
Elderly patients: retrospective subgroup analysis 2nd line treatment									
JMEI (Weiss, 2006)[91]	OS: superiority and noninferiority design	Pemetrexed	47	5.0	4.6*	9.5	20.4	0.86 (0.53–1.42)	NR
		Docetaxel	39	5.6	2.9*	7.7	23.1		
BR21 (Wheatley-Price, 2008)[92]	OS: superiority design	Erlotinib	112	7.6	3.0	7.6	NR	0.92 (0.64–1.34)	0.67
		Placebo	51	NR	2.1	5.0	NR		
PS2 patients: 1st line prospective treatment									
(Lilenbaum, 2008)[93]	Phase II design	Erlotinib	52	4	1.91	6.6	NR	1.45 (0.98–2.15)	0.063
	Median PFS	Carboplatin + paclitaxel	51	12	3.52	9.7	NR	1.73† (1.09–2.73)†	0.018†
STELLAR 3 (Langer, 2008)[94]	OS: superiority design	Carboplatin + paclitaxel poliglumex (PPX)	199	20	3.9*	7.8	31	NR	0.769
		Carboplatin + paclitaxel	201	37	4.6*	7.9	31		
PS2 patients: retrospective subgroup analysis 1st line treatment									
CALGB 9730 (Lilenbaum, 2005)[88]	OS: superiority design	Carboplatin + paclitaxel	49	24	NR	4.7	18	0.60 (0.40–0.91)	0.016
		Paclitaxel alone	50	10	NR	2.4	10		

CALGB indicates Cancer And Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; MILES, Multicenter Italian Lung Cancer in Elderly patients study; STELLAR, Selected Targeted Efficacy in Lung cancer to Lower Adverse Reactions; PS2, Performance status 2; HR, hazard ratio; OS, overall survival PFS, progression-free survival.

*Time to progression.

†Values for overall survival.

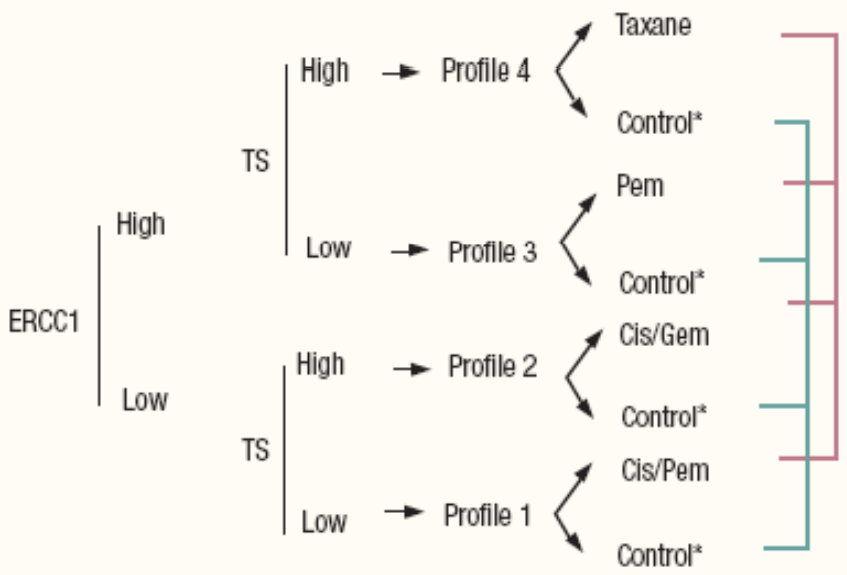
Clin Pulm Med 2009;16: 157–71

Individualizing Chemotherapy for NSCLC

THE FUTURE

Personalized treatments – biomarker based treatment decisions

Figure **Study Design of ITACA: Pharmacogenomic-Driven Adjuvant Study Assessing ERCC1 and TS**

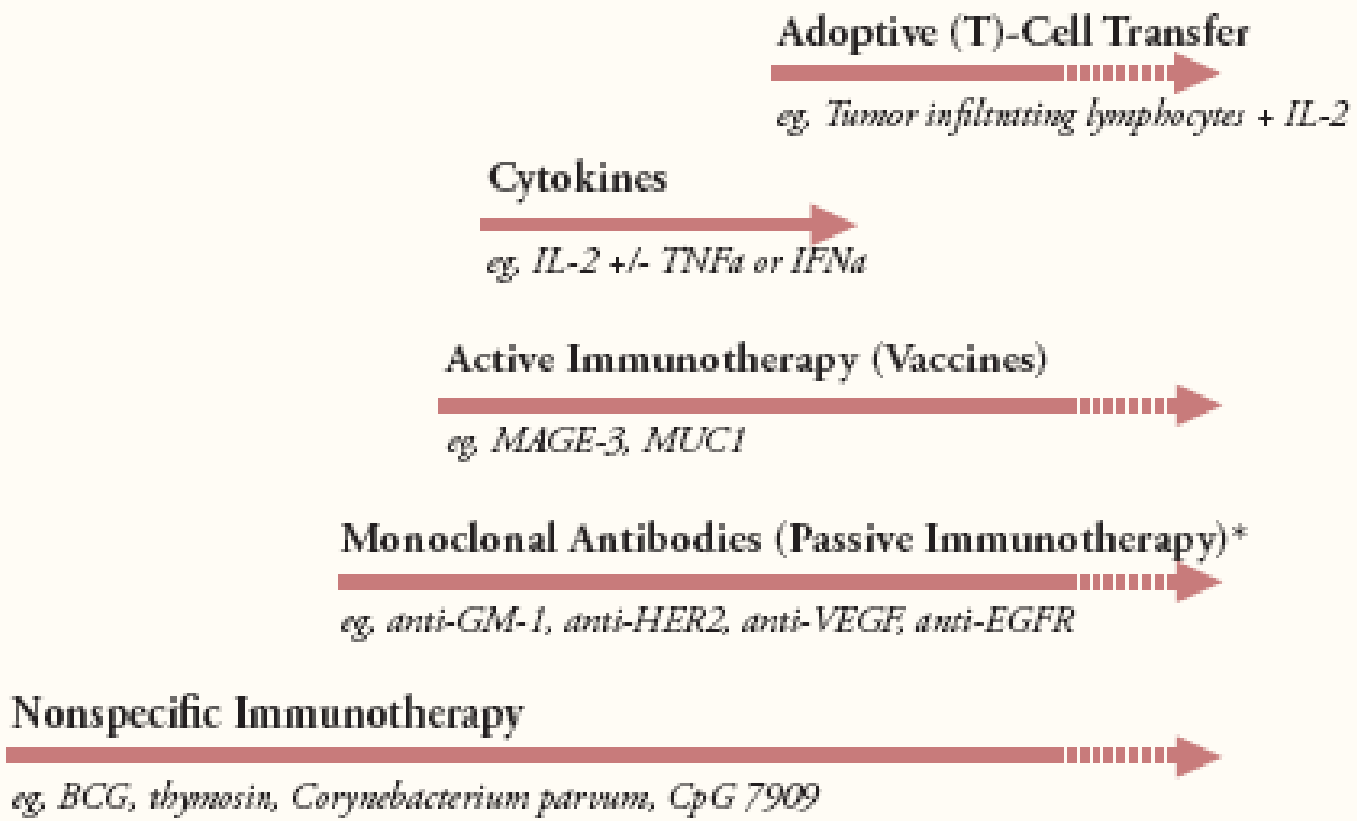


High/low ERCC1 and TS selected according to median level of mRNA expression in historical series.
*Investigator choice of a platinum-based doublet.
Abbreviations: Cis = cisplatin; ERCC1 = excision repair cross-complementing gene-1; Gem = gemcitabine; ITACA = International Tailored Chemotherapy Adjuvant; Pem = pemetrexed; TS = thymidylate synthase

Clinical Lung Cancer, Vol. 10, S35-S40, 2009

IMMUNOTHERAPY

Figure 2 **Immunotherapy Studies in Lung Cancer**



*Monoclonal antibodies are beyond the scope of this review and have been discussed elsewhere.[68,69]

Abbreviations: BCG = bacille Calmette-Guérin; EGFR = epidermal growth factor receptor; IFN = interferon; IL = interleukin; MAGE = melanoma antigen; MUC1 = mucin 1; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor

Clinical Lung Cancer, 99-105, 2009

CANCER VACCINES

Table 1 Non–Small-Cell Lung Cancer Vaccine Trials

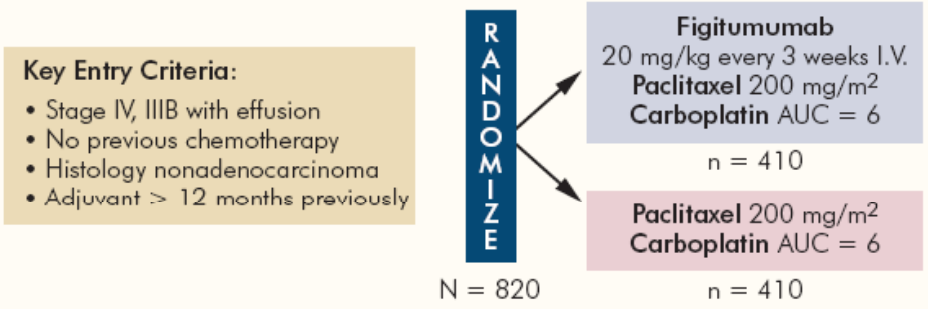
Vaccine Type	Vaccine Trial	Patient Population	Phase
Non–Antigen-Specific	Autologous tumor cell with BCG[10-17]	Resected NSCLC	Pilot study
	C parvum vaccine[18,19]	Resected NSCLC	Randomized trial
	SRL172 with **Mitomycin**, **Vinblastine**, and **Cisplatin** or **Carboplatin**[20]	Stage III-IV NSCLC, untreated	Phase III
	CTLA-4–blocking antibody[23-25]	NSCLC, renal cell carcinoma, pancreatic cancer, melanoma	Phase II
Tumor Antigen Based	MAGE-3 vaccine[30]	Stage IB and II NSCLC, resected	Phase III
	MAGE-3 dexosome[28]	Stage III-IV NSCLC, previously treated	Phase I
	EGF[32]	Stage IIIB-IV NSCLC, previously treated	Pilot study
	MUC1[34]	Stage IIIB-IV NSCLC, 1 previous line of therapy	Phase II
	Ras vaccine[33,35]	Advanced-stage colorectal, pancreatic, and lung cancer	Phase I
Cell Based			
Dendritic cell	Dendritic cells with CEA652[29]	Metastatic gastrointestinal cancer or NSCLC, previously treated	Pilot study
	Dendritic cells with irradiated 1650 cells[31]	Stage IA-IIIB NSCLC, treated with curative intent	Pilot study
Allogeneic tumor cell	Human leukocyte antigen–A gene-modified allogeneic adenocarcinoma cell line[27]	Stage IIIB-IV NSCLC, recurrent, previously treated	Phase I
	α-1,3-galactosyltransferase–expressing allogeneic tumor cell line[26]	Stage IIIB-IV NSCLC, previously treated	Phase I
Autologous tumor cell	Autologous tumor cell transfected with GM-CSF containing adenovirus[22]	Metastatic NSCLC, previously treated	Phase I
	Autologous tumor cell with bystander GVAX®[21]	Stage IB-IV NSCLC, previously treated	Phase I/II

Clinical Lung Cancer, 99-105, 2009

TARGETING INSULIN LIKE GROWTH FACTORS

Figure 3 **Study 1016: Phase III Trial of Paclitaxel/Carboplatin with or Without Figitumumab in First-Line Nonadenocarcinoma Non–Small-Cell Lung Cancer**

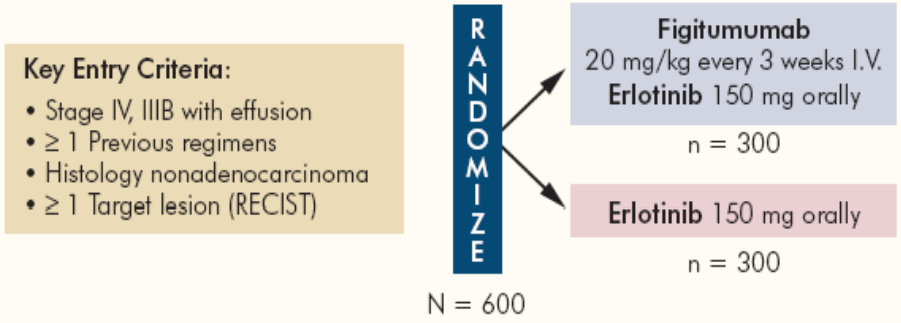
Title Design	Endpoints	Stratification	Study Sites	Start
Multicenter, randomized, open-label	Primary: OS Secondary: PFS, ORR, safety, QOL, biomarkers, pharmacoeconomics	• Region • Stage (IIIB vs. IV) • Adjuvant therapy (yes/no)	Worldwide	Second quarter 2008



Abbreviations: AUC = area under the curve; I.V. = intravenously; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; QOL = quality of life

Figure 4 **Study 1018: Phase III Trial of Erlotinib with or Without Figitumumab in Nonadenocarcinoma Non–Small-Cell Lung Cancer**

Title Design	Endpoints	Stratification	Study Sites	Start
Multicenter, randomized, open-label	Primary: OS Secondary: PFS, ORR, safety, QOL, biomarkers	• Sex • Geographical region • PS	Worldwide	Second quarter 2008



Abbreviations: I.V. = intravenously; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; QOL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors

Figitumumab (CP-751,871) ,fully human immunoglobulin G2 monoclonal antibody highly potent and specific against insulin-like growth factor-1 receptor.

Recent data suggest that figitumumab might be active in combination with platinum doublets for the treatment of chemotherapy-naive NSCLC

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TARGETED THERAPY : FUTURE

Target	Agents
Angiogenesis	AEE-788, AG-013736, AMG 706**, bevacizumab*, cediranib (AZD2171)**, CP-547632, sorafenib**, sunitinib**, vandetanib (ZD6474)**, vatalanib**
EGFR	Cetuximab**, erlotinib*, gefitinib*
Antisense oligonucleotides	Oblimersen**
Apoptosis	Exisulind**
Retinoid X receptor agonist	Bexarotene**
Proteasome inhibition	Bortezomib
Vaccines	Dendritic cell, GM-CSF modified
mTOR inhibitors	AP23573, everolimus (RAD-001), temsirolimus (CCI-779)

*Approved for use; **phase III trials; other agents are in phase II clinical trials.
EGFR, epidermal growth factor receptor; GM-CSF, granulocyte macrophage colony-stimulating factor; mTOR, mammalian target of rapamycin.

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CONCLUSIONS

- Despite recent therapeutic improvements, overall survival for most patients with lung cancer remains modest
- The preferred and recommended therapeutic approach is surgery alone for stage IA while it is surgery with adjuvant chemotherapy for stages II-IIIA and possibly IB
- Neoadjuvant chemotherapy followed by surgery may be considered for a select subgroup of patients with stage IIIA
- Advanced-stage NSCLC and a preserved performance status, platinum-based doublets are standard of care
- Single-agent therapy remains the standard for elderly patients and patients with a poor performance status
- Targeted therapy although impressive still has long way to go before it is accepted as routine