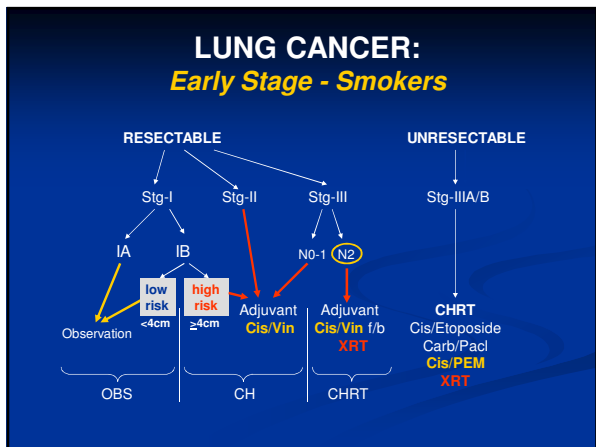


Molecular Markers to Predict Response to Chemotherapy in Lung Cancer

Saturday, April 17th, 2010

Rodolfo E. Bordon, MD





International Adjuvant Lung Cancer Trial (IALT)

1,867 patients. 148 centers, 33 countries.
 Cisplatin-based combinations: etoposide = 56.5%; vinorelbine = 26.8%
 (Compliance: 74%).
 Median follow-up: 56 months.

	5-yrS
Chemo (935)	44.5%
Observ (932)	40.4%
pValue	<0.03
Death HR	0.86

↓

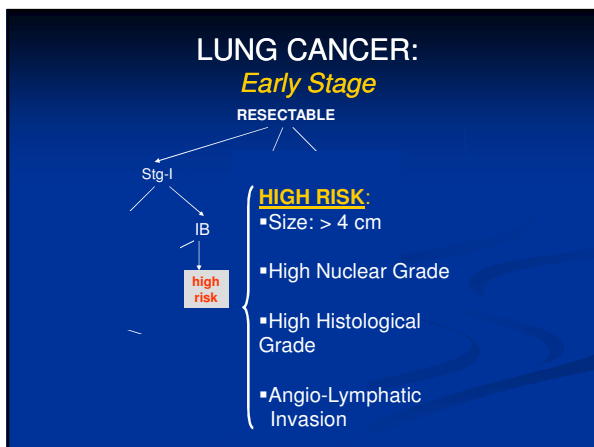
Largest benefit: Stage-III; < 65 y/o
 PORT: YES

Chemo, chemotherapy; observ, observation; HR, hazard ratio.

The International Adjuvant Lung Cancer Trial Collaborative Group. *N Engl J Med* 2004;350:351-360.

Stage Ib

HIGH RISK



Management of TNM Stage IB

	Stage	Therapy	Study result	Tumors	HR	pValue
IALT 2004	I/II/IIIA	Cis-based	POS	High ERCC1/MSH2	0.67	<0.006
CALGB 9633 2005	[^] IB	Carb/ Pacl	NEG	>4cm	0.69	0.043
ANITA 2007	[^] IB/II/IIIA	Cis/ Vinor	POS (but Ib)	>4cm poorly differ.	0.73	0.040

[^]Unplanned subset analysis; Cis-based, cisplatin-based; Carb/Pacl, carboplatin/paclitaxel; Cis/Vinor, cisplatin/vinorelbine; POS, positive; NEG, negative; HR, hazard ratio.

Strauss et al. *J Clin Oncol* 2008;26:5043-5051; Douillard JY, et al. *J Clin Oncol* 2005;23(16S): A-7013; Soria J, et al. *Journal of Clinical Oncology* 2006;24(18S): A-7010.

**Genetic profiling (by IHC) and Adjuvant Chemotherapy:
IALT (Cisplatin-based)**

761 pts.; ERCC1 (+) (DNA repair enzyme)

OS	ERCC1 (+) (N = 335)	ERCC1 (-) (N = 426)
Chemotherapy	HR: 1.18 p=0.29	HR: 0.67 p<0.006
Observation	HR: 0.65 p<0.008	HR: 1.0

HR, hazard ratio.

Soria J, et al. Journal of Clinical Oncology 2006;24(18S): A-7010.

**Genetic profiling (by IHC) and Adjuvant Chemotherapy:
IALT (Cisplatin-based)**

MSH2 enzyme required to repair cisplatin-DNA lesions

OS	MSH2(+)	MSH2(-)	MSH2(-) /ERCC1(-)
	257 (38%)	416 (62%)	--
673 tumors Chemoth.	*HR=1.12 p=0.48	*HR=0.76 p=0.03	*HR=0.65 p=0.01
Observation	*HR=0.66 p=0.01	--	--

Fouret P, et al. Journal of Clinical Oncology 2009;27(18S): CRA-7502.

**Genetic profiling (by IHC) and Adjuvant Chemotherapy:
IALT (Cisplatin-based)**

MSH2 enzyme required to repair cisplatin-DNA lesions

OS	MSH2(+)	MSH2(-)	MSH2(-) /ERCC1(-)
	N = 257 (38%)	N = 416 (62%)	--
673 Tumors Chemotherapy	*HR=1.12 p=0.48	*HR=0.76 p=0.03	*HR=0.65 p=0.01
Observation	*HR=0.66 p=0.01	--	--

Conclusions: MSH2 expression may predict long term benefit from cisplatin-based adjuvant chemo, and may be combined with ERCC1.

Fouret P, et al. Journal of Clinical Oncology 2009;27(18S): CRA-7502.

**Genomics and Prognosis of Early NSCLC:
Lung Metagene Model**

Method: 89 pts. initial retrospective DNA microarray (*genes that predict recurrence in early NSCLC*) on long term survivors. Blinded validation in previously treated pts on trials.

Results: Accuracy: 79%
PPV: 79%
NPV: 80%

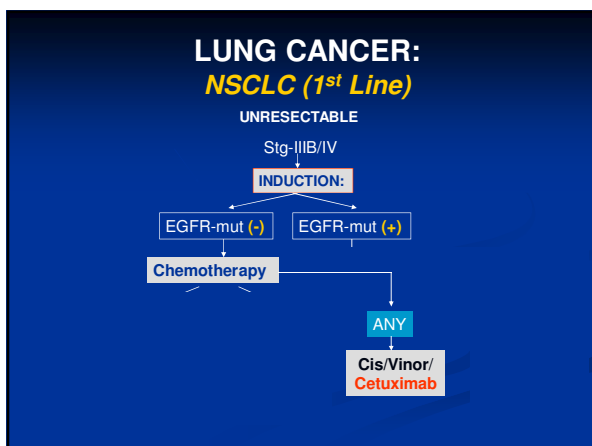
Stg-I	RISK		
	low	Inter	high
1-yS	93%	70%	<10%

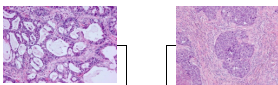
Good prognosis: 76%
Bad prognosis: 24%

Harpole DH, et al. Journal of Clinical Oncology 2006;24(18S):A-7026.

Advanced NSCLC

INDUCTION THERAPY





	AC	SCC
<u>Oncogenes point mutations</u>		
K-ras	high	low
<u>Gene overexpression</u>		
HER2/Neu	high	low
COX-2	high	low
<u>Gene methylation</u>		
APC	high	low
CDH13	high	low
RAR-beta	high	low

Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. IARC Press. 2004:35-44.

Importance of Histology in the Management of NSCLC

PAST: Sub-classification of epithelial lung carcinoma

MORPHOLOGY	IHC
Adenocarcinoma	TTF-1
Squamous cell carcinoma	TP63

(thyroid transcription factor-1)

PRESENT: New international lung adenocarcinoma classification

- Develop criteria for diagnosis of adenocarcinoma in small biopsies and cytology
- Characterize **BAC sub-types**

Travis WD, et al; Journal of Thoracic Oncology, in press.
Ring, BZ, et al. Modern Pathology 2009; 22, 1032-1043.

Novel 5-antibody IHC Subclassification of Lung Carcinoma

Background:
Tissue amount from needle biopsy: **600 μ**
Error rates: **25%** when diagnosis based on needle biopsy specimens

Study: 551 surgical lung carcinoma specimen
Five antibodies, targeting proteins TRIM29, CEACAM5, SLC7A5, MUC1, and CK5/6

Results:	%-Ab test	TTF-1/TP63
misclassification rates	4.1%	3.5%
unclassifiable	11%	22%

Ring, BZ, et al. Modern Pathology 2009; 22, 1032-1043.

Pemetrexed/Cisplatin vs. Gemcitabine /Cisplatin in 1st-Line Advanced NSCLC

Multicenter, randomized, open-label study conducted to compare the overall survival following treatment with pemetrexed/cisplatin vs. gemcitabine/cisplatin

Randomization Factors

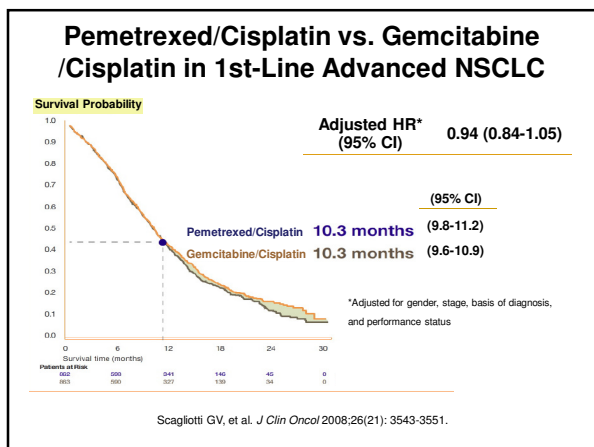
- ECOG PS
- Stage
- History of brain metastases
- Gender
- Pathological diagnosis (histological vs cytological)

RANDOMIZE

Pemetrexed (N=862)
500 mg/m² IV q21d
Plus Cisplatin 75 mg/m² IV Day 1

Gemcitabine (N=863)
1250 mg/m² IV on Day 1 and Day 8
Plus Cisplatin 75 mg/m² IV Day 1

Scagliotti GV, et al. *J Clin Oncol* 2008;26(21): 3543-3551.



Pemetrexed/Cisplatin vs. Gemcitabine /Cisplatin in 1st-Line Advanced NSCLC

Histology Subgroup	Median OS (Months)		HR
	Pemetrexed/Cisplatin	Gemcitabine/Cisplatin	
Nonsquamous NSCLC (1252)	11.0	10.1	0.84
AdenoCa(847)	12.6	10.9	0.84
Large Cell (153)	10.4	6.7	0.68
Other (252)	8.6	9.2	1.12
Squamous Cell (473)	9.4	10.8	1.22

Scagliotti GV, et al. *J Clin Oncol* 2008;26(21): 3543-3551.

VEGF Levels as A Predictive Biomarker of Efficacy in NSCLC Pts Treated with Vandetanib

ZACTIMA (*vandetanib*) improved PFS in advanced NSCLC in three randomized phase II studies (1. vandetanib vs. gefitinib; 2. docetaxel ± vandetanib; 3. carboplatin/paclitaxel ± vandetanib)

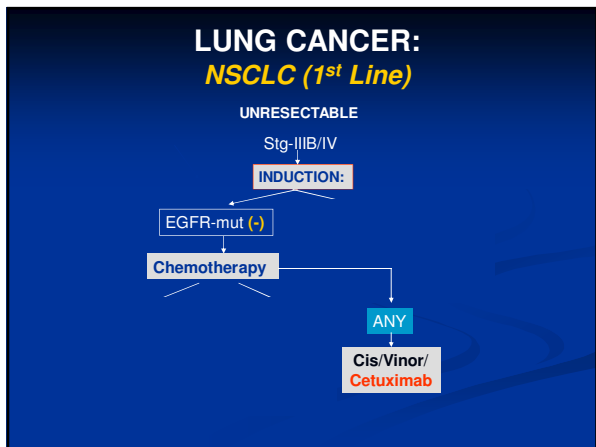
Study: exploratory analysis of baseline circulating VEGF, PFS and OS.

Results:

low baseline circulating **VEGF:**

- better PFS & OS in **1, and 2**
- similar PFS & OS in **3**

Ryan A. Biomarker Web Symposia. October 8, 2009

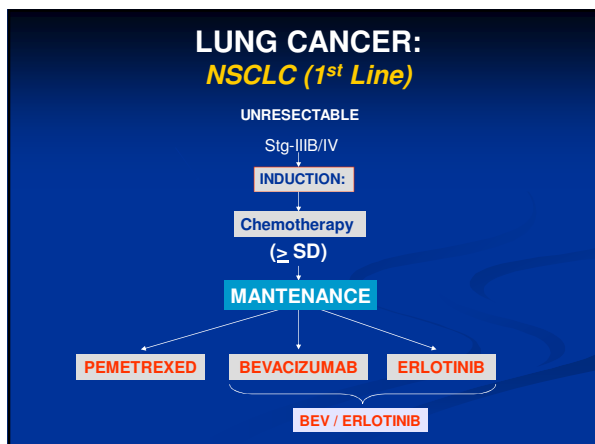


MAINTENANCE THERAPY

Advanced NSCLC

MAINTENANCE THERAPY

Advanced NSCLC



PEMETREXED

Maintenance Pemetrexed in Advanced NSCLC

Design: randomized Phase III, double blind study

Stage IIIb/IV ≥SD post-Platinum- Based* induction x 4 cycles	R A N D O M I Z E D 2:1	663 patients	OS	PFS	ORR
		Pemetrexed 500 mg/m ² Folic Acid/B12/DEX	13.4 months	4.3 months	51.7%
		Placebo every 21 days	10.6 months	2.6 months	33.3%
		HR	0.79	---	---
		<i>pValue</i>	<i>0.012</i>	<i>0.0001</i>	<i>0.001</i>

*Carboplatin/cisplatin +
paclitaxel/gemcitabine/docetaxel

OS, overall survival; PFS, progression-free survival;
ORR, objective response rate; DEX, dexamethasone; HR, hazard ratio.

Belani CP, et al. Journal of Clinical Oncology 2009;27(18S): CRA-8000.

Maintenance PEM in advanced NSCLC:
per histology

	Median OS in mo		
	PEM	Plac	pVal/HR
Non-Sq	15.5	10.3	0.002/ 0.70
Adeno	16.8	11.5	0.025/0.73
Large cell	8.4	7.9	0.964/0.98
Other	11.3	7.7	0.025/0.61
Squa	9.9	10.8	0.678/1.07

Under performers: SqCCA, Asians.
Post-study therapy: PEM 52%; Plac 67%.

Belani CP, et al. *Journal of Clinical Oncology* 2009;27(18S): CRA-8000.

Maintenance Therapy in Advanced NSCLC

Individualized as per patient:
SYMPTOMATIC: yes

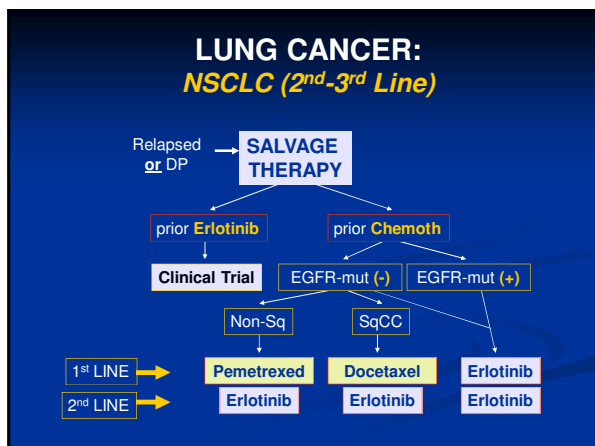
ASYMPTOMATIC: no

ADENO CA **Pemetrexed HR for MOS: 0.452**

EGFR mut **Erlotinib HR for PFS: 0.10**
(Learn **after** chemo induction).

SALVAGE THERAPY

Advanced disease



Adenocarcinoma Histology Affecting Survival in NSCLC Treated with Pemetrexed

Design: retrospective analysis, phase-III trial, advanced NSCLC, salvage chemotherapy

Rational: preclinical data suggesting lower thymidylate synthase (TS) expression confers increased sensitivity to pemetrexed (Sigmund J, et al. *Biochem Pharmacol* 2003; 66:431-38. Ceppi P, et al. *Cancer* 2006; 107:1589-96)

Results:

non-squamous histology	OS	squamous histology	OS
pemetrexed 500 mg/m ²	9.3 mo	pemetrexed 500 mg/m ²	6.2 mo
docetaxel 75 mg/m ²	8.0 mo	docetaxel 75 mg/m ²	7.4 mo
HR	0.778	HR	1.563

OS, overall survival; mo, months; HR, hazard ratio

Peterson P, Park K, Fossella F, et al. ECCO 2007, Abstract # 6521

ERCC1 Predicts PFS and OS in NSCLC Treated with Platinum-Based Chemotherapy: 2nd Line-Retrospective Trial

67 pts, IHC to examine protein expression in resected lung tumor samples, upon cancer progression

	IHC	PFS	OS
ERCC1 (-)	38:67	44 wks	73 wks
ERCC1 (+)	29:67	26 wks	44 wks
P53 (-)	32:67	37.5 wks	70 wks
P53 (+)	35:67	36 wks	62 wks

IHC, immunohistochemistry ; PFS, progression-free survival; OS, overall survival, wks; weeks.

Conclusion: ERCC1 expression by IHC may be useful in planning personalized chemotherapy (and predicting OS) in NSCLC at the time of recurrent tumors, after curative R0.

Azuma K, et al. *Cancer Sci* 2007 Sep;98(9):1336-43.

Conclusions:

- The use of molecular markers to predict response to chemotherapy in non-small cell lung carcinoma (NSCLC) is still experimental
- ERCC1 is a commercially available prognostic and predictive molecular marker of response to platinum compounds
- Partially validated in advanced NSCLC in prospective phase II trials. Phase III trials ongoing
- Potential candidate to help identify patients with early stage disease that can be spared adjuvant chemotherapy

Conclusions:

- Accurate characterization of histological sub-types of NSCLC is currently the most helpful strategy to maximize therapy selection
- Novel technologies (miRNA-Based Approach) are being validated to maximize the sub classification of lung cancer
