

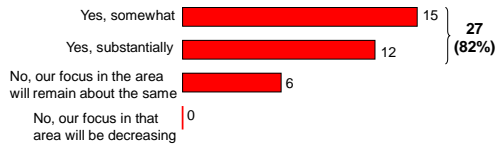
Molecular Markers to Predict Response to Chemotherapy in Lung Cancer

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Pharmacogenomics: *Present and Future*

Will your company or lab be expanding its pharmacogenomics-based research or development efforts in the near future?



CHI Insight Pharma Reports. June 2009. Pharmacogenomics: Delivering on the Promise.

Early stage NSCLC

ADJUVANT THERAPY

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**

673 Tumors	OS	MSH2(+) N = 257 (38%)	MSH2(-) N = 416 (62%)	MSH2(-) /ERCC1(-) --
	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.

**Molecular Profiling of Cancer:
Algorithm
NSCLC**

Early

Stage	Clinical features	Test/s	Results	Treatment decision
IB (post-Op)	< 4cm, poor prognosis (angiolymph, high pathology grade)	ERCC1	+	Observation (no adjuvant chemotherapy)
			-	Cisplatin-based adjuvant chemotherapy

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

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

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

Stage I	RISK		
	LOW	INT	HIGH
1-Year Survival	93%	70%	<10%

Good prognosis: 76%
Bad prognosis: 24%

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

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)

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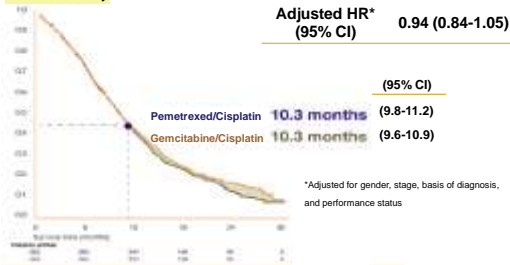
Pemetrexed (N=862)
 500 mg/m² IV q21d
 Plus Cisplatin 75 mg/m² IV Day 1

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

Survival Probability



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

**Phase III Trial of Bevacizumab in NSCLC:
ECOG 4599-Efficacy by Gender**

Toxicity - PBC Arm			
	HTN %	Const %	Abd Pain %
Male	4.2	1.4	0.9
Female	9.9	4.7	5.2
<i>pValue</i>	0.02	0.05	0.01

PBC, Paclitaxel/carboplatin/bevacizumab; HTN, hypertension;
Const, constipation; Abd, abdominal.

Brahmer JR, et al. *J Clin Oncol* 2006;24(18S): A-7036.

**Phase III Trial of Bevacizumab in NSCLC:
ECOG 4599-Efficacy by Age**

Patients: 224:850 (26.3%) patients \geq 70 years old on E4599

Results:

	ORR (%)	PFS (months)	OS (months)	Grade 3/5 Toxicities
PCB	29	5.9	11.3	87%
PC	17	4.9	12.1	61%
<i>pValue</i>	0.067	0.063	0.4	<0.001

ORR, objective response rate; PFS, progression-free survival; OS, overall survival;
PBC, Paclitaxel/carboplatin/bevacizumab; PC, Paclitaxel/carboplatin.

Ramalingam SS, et al. *J Clin Oncol* 2007;25(18S): A-7535.

Approaches to Limit VEGF Activity

VEGF and its receptors play essential role in tumor proliferation.

- anti-VEGF recombinant humanized monoclonal antibody:
Bevacizumab
- Small molecule targeting VEGF tyrosine-kinase activity:
Vandetanib
Sorafenib
Sunitinib
- VEGF Trap
- Vascular disrupting agents:
ASA404

Rossi A, et al. *Curr Med Chem* 2009;16(30):3919-30.

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

Individualized Therapy in Advanced NSCLC:

1st Line-Prospective Trial

60 pts with stage IIIB/IV NSCLC.
ERCC1 and RRM1 gene expression by RT-PCR.

ERCC1	RRM1	treatment
low	low	Gem/cis
high	low	Gem/doc
low	high	Doc/cis
high	high	Doc/vino

Gem/cis, gemcitabine/cisplatin;
Gem/doc, gemcitabine/docetaxel;
Doc/cis, docetaxel/cisplatin;
Doc/vino, docetaxel/vinorelbine.

PR	12-Month		Median Survival (months)
	OS (%)	PFS (%)	
44	59	14	13.3
TAX-326	43.6		

PR, partial response; OS, overall survival;
PFS, progression-free survival.

Simon GR, et al. *J Clin Oncol* 2007;25(18S): A-7512; Simon GR, et al. *Int J Biochem Cell Biol*. 2007;39(7-8):1318-28.

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	PFS P = 0.0075 OS P = 0.0006
ERCC1 (+)	29:67	26 wks	44 wks	
P53 (-)	32:67	37.5 wks	70 wks	PFS P = 0.2465 OS P = 0.0289
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.

BRCA1

- BRCA1 as a differential modulator of chemosensitivity.
BRCA1 expression:
High: sensitivity to antimicrotubule drugs
(paclitaxel and vincristine)

Low: sensitivity to DNA-damaging agents
(cisplatin and etoposide) and radiotherapy
- Experimental models (breast and ovarian cancer):
 High: enhanced paclitaxel sensitivity
 *Low: aclitaxel and docetaxel resistance

*RNA-mediated inactivation of endogenous BRCA1

Clinical Data: NSCLC

EARLY STAGE: SCAT (Spanish customized adjuvant trial
Design: 84 patients with R0 resected, N1-2 NSCLC.

RANDOMIZED	Groups (N)	Therapy	Median OS
	High BRCA (11)	Docetaxel	NR
	Int BRCA (29)	Docetaxel/Cisplatin	NR
	Low BRCA (44)	Cisplatin/Gemcitabine	25.6 months

ADVANCED STAGE:

RANDOMIZED	Groups (N)	Therapy	Median OS
	High BRCA (38)	Docetaxel	11 months
	Int BRCA (40)	Docetaxel/Cisplatin	9 months
	Low BRCA (33)	Cisplatin/Gemcitabine	11 months

Cobo M, et al. Journal of Clinical Oncology 2008;26(20S): A-7533.
 Rosell R, et al. Journal of Clinical Oncology 2008;26(20S): A-8037.

Molecular Profiling of Cancer: Algorithm NSCLC

Advanced

Stage	Clinical features	Test/s	Results	Treatment decision
IIb/IV	Squamous	ERCC1	+	Platinum-Gemcitabine
			-	Taxane-Gemcitabine
	Non-Squamous		+	Platinum-Pemetrexed
			-	Taxane-Pemetrexed
IIb/IV	Any histology	None	N/A	Cetuximab-based triplet

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

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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	---	---
pValue	0.012	0.0001	0.001

*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			Median PFS in mo		
	PEM	Plac	pVal/HR	PEM	Plac	pVal/HR
Non-Sq	15.5	10.3	0.002/0.70	4.37	1.84	<0.00001/ 0.47
Adeno	16.8	11.5	0.025/0.73	4.60	2.66	<0.00001/ 0.51
Large cell	8.4	7.9	0.964/0.98	4.53	1.45	0.104/0.40
Other	11.3	7.7	0.025/0.61	4.11	1.58	0.0001/0.44
Squa	9.9	10.8	0.678/1.07	2.43	2.50	0.896/1.03

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
