

**Vimentin (EMT Marker Protein) Score
Predicts Resistance to Erlotinib and
Radiotherapy for Patients with Stage III
Non-Small Cell Lung Cancer On A
Prospective Phase II Trial**

Ritsuko Komaki, M.D. FACR, FASTRO

***The University of Texas MD Anderson Cancer
Center, Houston, TX***

Disclosure

Dr. Komaki was supported by

- 1. Genentech (Erlotinib provider)*
- 2. US Department of Defense (DOD)*
- 3. NCI: NCI Trial Identifier #: NCI-2012-01761*

Introduction and Background

Erlotinib has Radiation Sensitization. However patients with NSCLC get resistant to Erlotinib and RT. Vimentin (EMT marker protein) might be the predictor for the resistance to Erlotinib and chemoradiotherapy for patients with stage III non-small cell lung cancer (NSCLC).

Materials & Methods

- **48 stage III NSCLC patients were prospectively enrolled to phase II clinical trial, ID 2005-1023, from 3/2008 through 6/2010.**
- **Eligibility :**
 - ❖ **Karnofsky's performance status (KPS) \geq 70,**
 - ❖ **Weight loss \leq 5% over past 3 months,**
 - ❖ **FEV₁ \geq 1.0 L, adequate hematologic, hepatic, and renal functions.**
- **Available patients for immunohistochemical analysis = 22**
- **Exclusion criteria:**
 - **No tissue specimens = 25**
 - **Taken off study = 1**

(This patient expired due to gall bladder operation)

Methodology

- For these analysis, the tissue specimens were histologically assessed for the **presence of malignant cell** content, and the presence of **enough tissue** for biomarkers tests.
- Vimentin: Stained by **Immunohistochemistry (IHC)** of cytoplasm.

Patients Characteristics

Characteristics	Subgroup	No. of patients (n= 22)	%
Age (year)	Median age	63 (46 – 70)	
	≤ 63	11	50.0
	> 63	11	50.0
Gender	Male	15	68.2
	Female	7	31.8
Race	White	19	86.4
	Hispanic	2	9.1
	Other	1	4.5
KPS	80	7	31.8
	90	14	63.6
	100	1	4.5
Smoking Hx	Current smoker	4	18.2
	Former smoker	16	72.7
	Non-smoker	2	9.1
Stage	IIIA	11	50.0
	IIIB	11	50.0
Pathology	Squamous	7	31.8
	Adeno	10	45.5
	NSC	4	18.2
	Large cell	1	4.5

Treatment Schema of ID 2005-1023

Weeks 1-7

	Week 1							Week 2							Week 3							Week 4							Week 5							Week 6							Week 7						
Days	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Radiation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Carboplatin	C							C						C						C							C							C							C								
Paclitaxel	C							C						C						C							C							C							C								
Erlotinib	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T	T		

Weeks 8-11

Weeks 12-17

XRT: 63 Gy/35 Fx/7weeks; 1.8Gy/daily x 5

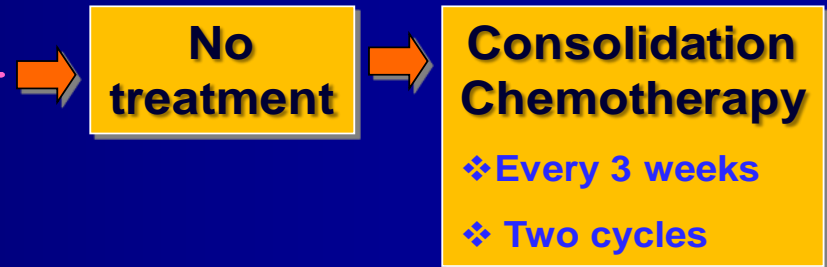
Concurrent Chemo RT

- ❖ Weekly x 7 weeks
- ❖ Day: 1, 8, 15, 22, 29, 36 & 43
- ❖ Paclitaxel: 45mg/m²
- ❖ Carboplatin: AUC=2
- (No Erlotinib on the same day of Chemo)



Concurrent Erlotinib / RT

- Erlotinib alone:
- ❖ over weekends x 7 weeks
 - ❖ Starting on day 2 with RT,
 - ❖ 150mg/m² ; p.o.
 - ❖ Daily



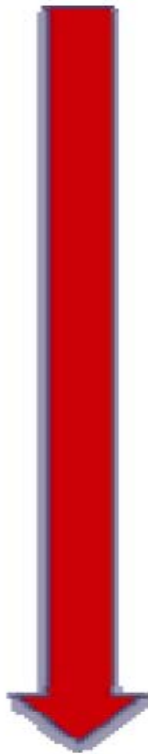
- ❖ Paclitaxel: 200 mg/m²,
- ❖ Carboplatin: AUC=6,

Vimentin Expression

Characteristics	Subgroup	No. of patients (%) (n= 22)		p-value
		Vimentin (cutoff level = 240)		
		Negative (<240) (n= 18)	Positive (≥ 240) (n= 4)	
Age (year)	≤ 63	9 (82)	2 (18)	1.00
	> 63	9 (82)	2 (18)	
Gender	Male	11 (73)	4 (27)	0.26
	Female	7 (100)	0 (0)	
Race	White	16 (84)	3 (16)	1.00
	Non-White	2 (67)	1 (33)	
KPS	< 90	6 (86)	1 (14)	1.00
	≥ 90	12 (80)	3 (20)	
Smoking Hx	Smoker	16 (80)	4 (20)	1.00
	Non-smoker	2 (100)	0	
Stage	IIIA	9 (82)	2 (18)	1.00
	IIIB	9 (82)	2 (18)	
Pathology	Adeno	8 (80)	2 (20)	1.00
	Non-Adeno	10 (83)	2 (17)	

Immunohistochemistry

H-score
0



300

Vimentin



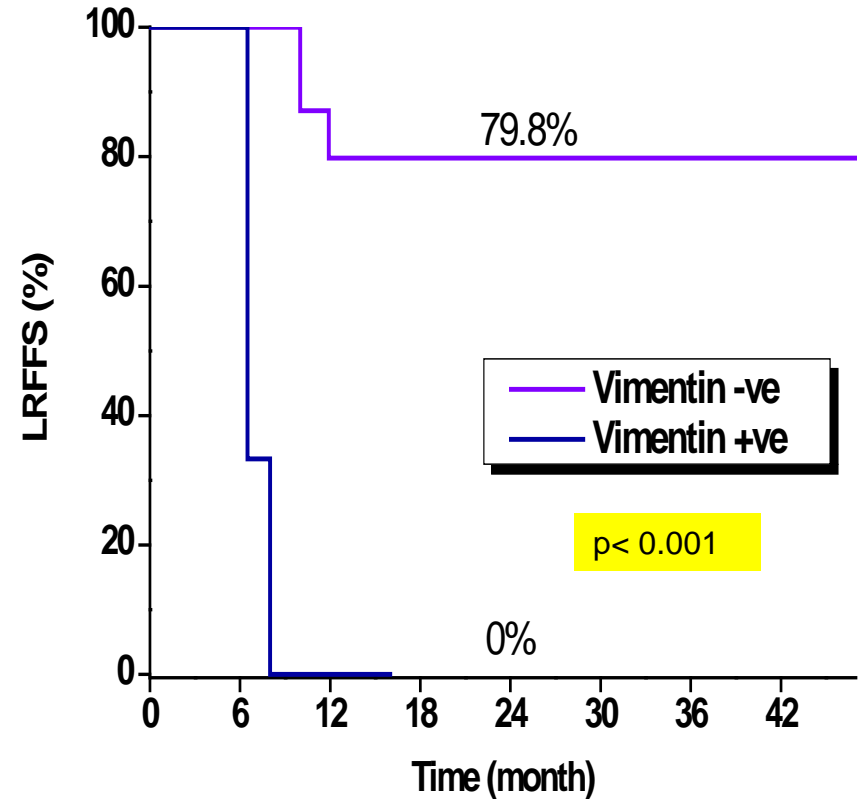
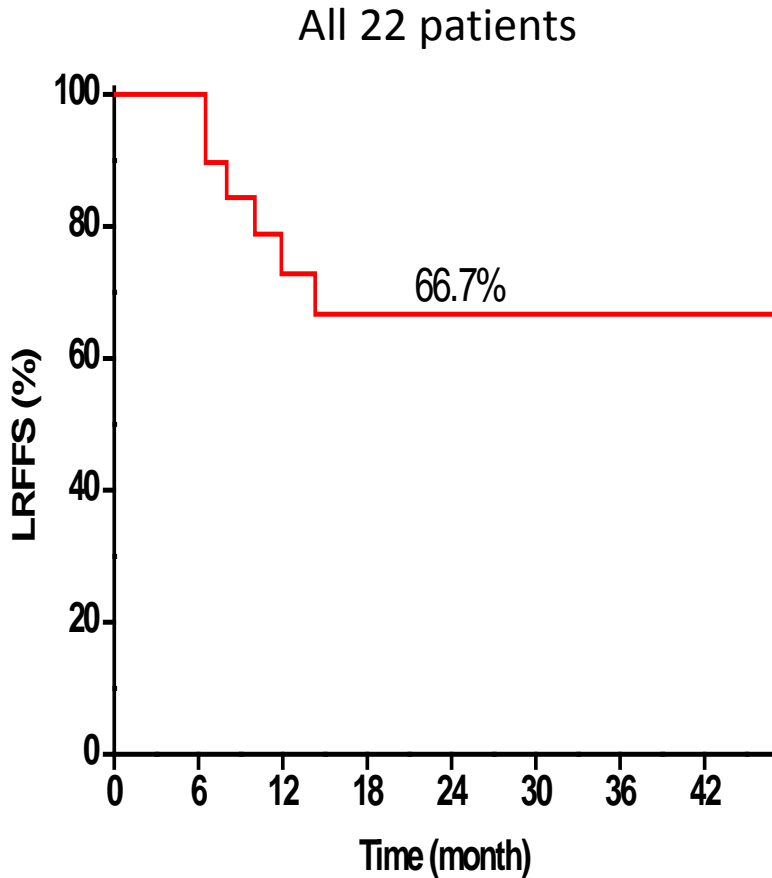
Vimentin positive:

cutoff level = 240

Expression Profiles of Vimentin

	No. of			No. of			No. of p	
Cytoplasm	patients		Cytoplasm	patients		Cytoplasm	atients	
intensity	(n= 22)	%	extension	(n= 22)	%	score	(n= 22)	%
0	13	59.1	≤ 30	2	9.1	0	13	59.1
1	2	9.1	31~50	2	9.1	1~99	2	27.3
2	3	13.6	51~99	2	9.1	100	3	13.6
3	4	18.2	100	16	72.7	> 240	4	16.0

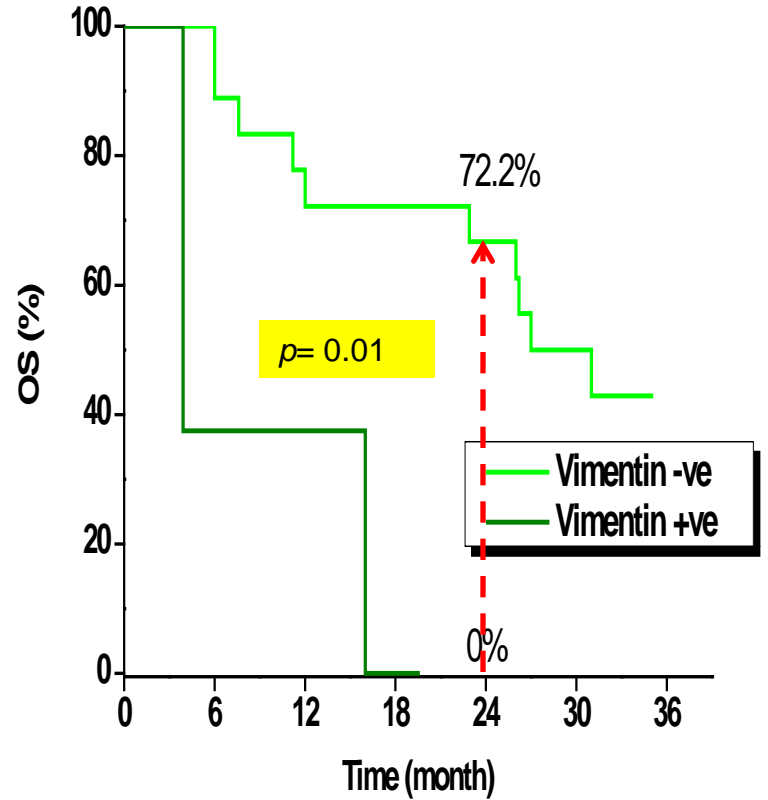
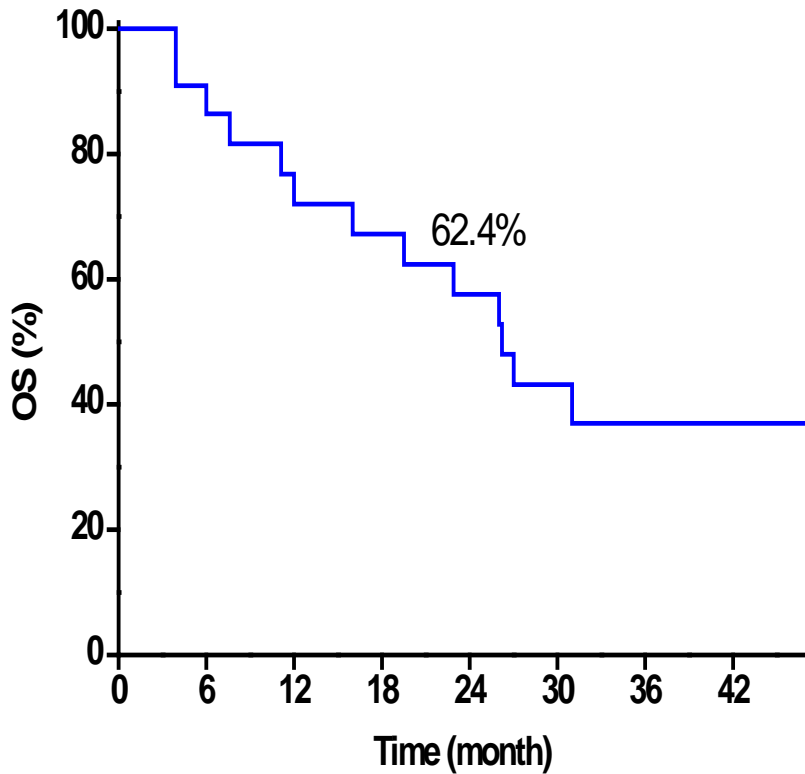
Locoregional Failure-Free Survival



locoregional failures : Recurrences in the primary tumor and/or regional lymph node.

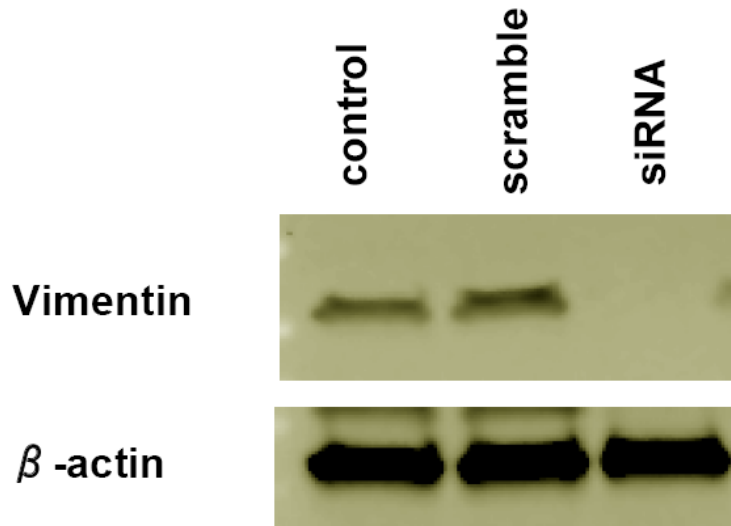
Overall Survival

All 22 patients

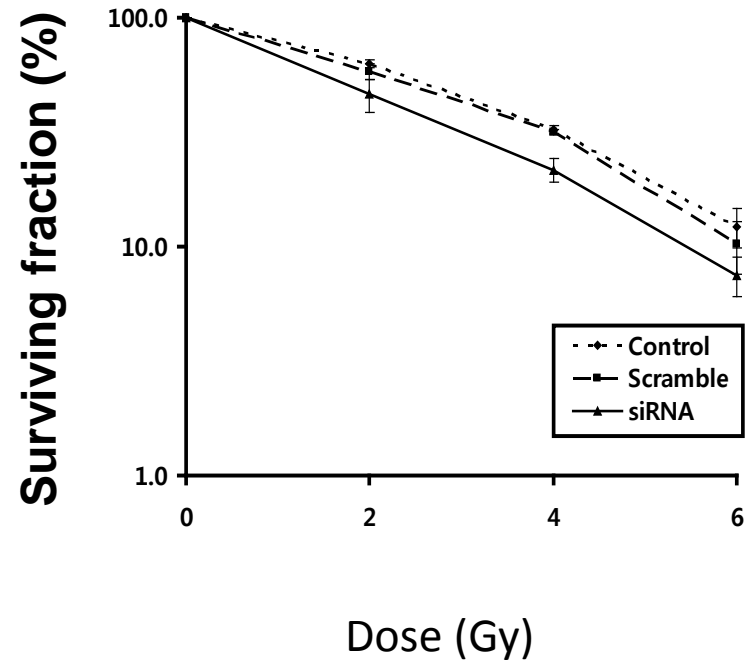


Knockdown of Vimentin Radiosensitizes H1299

(A) Western blotting for Knockdown of Vimentin with siRNA (small-interfering RNA)



(B) Clonogenic assay



Conclusions

- Vimentin expression might be used as a predictor for patients with stage III NSCLC who do not respond to **erlotinib and radiotherapy combined by chemoradiotherapy**, although we need validation with larger number of patients.
- Vimentin expression is associated with **radioresistance**, and can be tried to be the target to improve the efficacy of radiotherapy

Thank you

Acknowledgements

Yong Bae Kim , M.D.,

Ignacio Wistuba, M. D.,

Ximing Tang, M.D.,

Ray Meyn Jr, Ph.D. ,

K.Kian Ang, M.D. Ph.D.

Pamela K Allen, Ph.D. ,

Xiong Wei, M.D.,

J. Jack Lee, Ph.D.,

James D.Cox, M.D.,

George Blumenschein, M.D.,

James Welsh, M.D.,

Wuan Ki Hong, M.D.