CLINICAL OUTCOMES IN LUNG CANCER PATIENTS FROM 2009 TO 2013 IN AKITA RED CROSS HOSPITAL

Ryo Morita[1)], Hirokazu Kurokawa[1)], Mariko Asano[2)], Yuji Okuda[2)], Hidesato Odaka[1)], Hideki Kawai[3)], Kazuki Miura[4)] and Hiroshi Ito[2)]

(received 1 May 2014, accepted 11 August 2014)

[1)]Department of Respiratory Medicine, Akita Red Cross Hospital, Japan.
222-1, Nawashirosawa, Saruta, Kamikitate, Akita, 010-1406, Japan
[2)]Department of Cardiovascular and Respiratory Medicine, Akita University Graduate School of Medicine, Akita, Japan.
Hondo 1-1-1, Akita, 010-8543, Japan.
[3)]Department of Thoracic Surgery Akita Red Cross Hospital, Japan.
222-1, Nawashirosawa, Saruta, Kamikitate, Akita, 010-1406, Japan
[4)]Department of Respiratory Medicine, Sotoasahikawa Hospital, Japan.
142, Migota, Sotoasahikawa, Akita, 010-0802, Japan

Abstract

Background : The prevalence of deaths due to malignant tumors in Akita Prefecture was the highest in all of Japan from 1998 to 2013. In 2012, lung cancer caused the greatest number of cancer-related deaths in Akita Prefecture.

Purpose : To investigate the clinical outcomes of patients with lung cancer treated at Akita Red Cross Hospital.

Methods : Patients diagnosed with lung cancer for the first time and treated at Akita Red Cross Hospital from January 2009 to December 2013 were enrolled, and their clinicopathological factors were assessed.

Results and Conclusions : In total, 493 patients were enrolled (328 men, 165 women ; median age=70 years). There were 318 patients with adenocarcinomas, 104 with squamous cell carcinomas, 12 with adenosquamous cell carcinomas, seven with large-cell carcinomas, and 52 with small-cell carcinomas. Of the total patients, 237 underwent surgical treatment, and their 5-year survival rate was 66.5%. The remaining 256 patients received non-surgical treatment, and their median overall survival was 14 months. The reasoning behind the chemotherapy treatment strategy decisions were largely unclear. These findings highlight the need to develop a clear treatment strategy with regard to relevant objective factors.

Key words : Lung Cancer, Clinical Outcome, Chemotherapy

Introduction

Recently, malignant tumors have become the most common cause of death in Japan[1)]. The situation is similar in Akita Prefecture, where death due to malignant tumors has increased every year and peaked from 1998 to 2013. Until 2011, gastric cancer was the most common cause of deaths in Akita Prefecture ; in 2012, however, lung cancer caused the greatest number of deaths[2)]. In-

Address for correspondence : Ryo Morita, MD
Department of Respiratory Medicine, Akita Red Cross Hospital, Japan.
222-1, Nawashirosawa, Saruta, Kamikitate, Akita, 010-1406, Japan
TEL : 81-18-829-5000
FAX : 81-18-829-5255
E-mail : rmorita@med.akita-u.ac.jp

deed, despite surgical resection and the development of new chemotherapy regimens, many lung cancer patients suffer relapses and die[3].

In addition, recently patients with lung cancer have been treated differentially according to their histological subtype and/or mutation status. This change has been associated with the development of new drugs for lung cancer, particularly those targeting molecules[4]. Medical guidelines for lung cancer in Japan now recommend that physicians treat based on the histological subtype and mutation status of epidermal growth factor receptor (*EGFR*) and translocations involving genes encoding the echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma receptor tyrosine kinase (*EML4-ALK*)[5]. Moreover, targeted therapies for mutations of other driver genes, including *ROS1*, *RET*, and *HER2*, are in development[6].

The recommended regimens vary according to age and the Eastern Cooperative Oncology Group performance status (ECOG PS). The treatments for lung cancer will further diversify in the future. In this study, we investigated the clinical outcomes in lung cancer patients at Akita Red Cross Hospital from 2009 to 2013 in an effort to improve the treatment of lung cancer.

Materials and Methods

Patients diagnosed with lung cancer for the first time and treated at Akita Red Cross Hospital from January 2009 to December 2013 were enrolled in this study. Before treatment, we determined the age, gender, treatment received, side of the primary lesion, histological type, driver mutation, and clinical stage of all patients. After the patients underwent surgery, we determined the pathological stage and measured overall survival. Overall survival was also measured in patients who received non-surgical treatments.

We categorized the lung cancer patients who received chemotherapy and/or radiotherapy by histological type. We determined the regimens and measured overall survival.

All statistical analyses were performed using the JMP software (ver. 8.0 for Windows). Categorical data were compared using Fisher's exact probability test. Continuous variable data were compared using *t*-tests between each factor. Correlations of treatment and histological type with overall survival were determined using the Kaplan-Meier method and the log-rank test. Hazard ratios were determined using the Cox proportional hazards model. P values <0.05 were considered to indicate statistical significance.

Results

In total, 493 patients (328 men, 165 women) with lung cancer were enrolled in the study. Patient characteristics are listed in Table 1. The patients had a median age of 70 (range, 31-95) years. In total, 227 patients underwent surgery and 266 patients received non-surgical treatments ; 265 patients had a primary lesion in the right lung and 228 in the left lung.

Regarding cancer type, 318 patients had adenocarcinomas, 104 had squamous cell carcinomas, 12 had adenosquamous cell carcinomas, 7 had large-cell carcinomas, and 52 had small-cell carcinomas. Regarding driver mutations, 98 patients had *EGFR* mutations and 6 had *EML4-ALK* fusion genes.

According to clinical stage, 132 patients were stage IA, 48 were stage IB, 27 were stage IIA, 13 were stage IIB, 43 were stage IIIA, 31 were stage IIIB, and 199 were stage IV. These classifications were made according to the sixth and seventh editions of the General Rules for Clinical and Pathological Records of Lung Cancer.

We measured overall survival according to clinical stage (Fig. 1). Stages IA and IB were not defined. The 5-year survival rate was 81% in patients with stage IA and 56% in patients with stage IB cancer (stage IIA, 38 months ; stage IIB, 32 months ; stage IIIA, 31 months ; stage IIIB, 11 months ; and stage IV, 7 months).

We categorized the lung cancer patients into two groups according to treatment. Patient characteristics are listed in Table 2. We assessed the age, gender, side of the primary lesion, histological type, driver mutation, and clinical or pathological stage in the patients. No significant difference was seen between the surgical and non-surgical treatment groups in terms of age, gender, side of the primary lesion, or driver mutation.

In the surgical treatment group, there were 139 men

Table 1. Baseline characteristics of lung cancer patients in our hospital

	All patients (n=493)
	No. Patients (%)
Age, median (range)	70 (31-95)
Gender	
male	328 (66.5)
female	165 (33.5)
Treatment	
surgery	227 (46.0)
non-surgery	266 (54.0)
Side of primary lesion	
Right lung	265 (53.8)
Left lung	228 (46.2)
Histologic Type	
Adeno carcinoma	318 (64.3)
Squamous cell	104 (21.3)
Adenosquamous	12 (2.4)
Large cell	7 (1.4)
Small cell	52 (10.6)
Driver Mutation	
EGFR	110 (22.3)
EML4-ALK	6 (1.2)
Crinical / Pathologic Stage	
IA	132 (26.8)
IB	48 (9.7)
IIA	27 (5.5)
IIB	13 (2.6)
IIIA	43 (8.7)
IIIB	31 (6.3)
IV	199 (40.4)

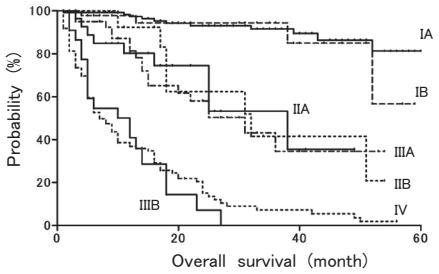

Fig. 1 Kaplan-Meier estimates of survival by clinical stage of lung cancer. The 5-year survival rate was 81% in patients with stage IA and 56% in patients with stage IB cancer (stage IIA, 38 months ; stage IIB, 32 months ; stage IIIA, 31 months ; stage IIIB, 11 months ; and stage IV, 7 months).

and 98 women, with a median age of 69 (range, 37-87) years. In the non-surgical treatment group, there were 189 men and 67 women, with a median age of 72 (range, 31-95) years.

In the surgical treatment group, 131 patients had a primary lesion in the right lung and 106 in the left lung. In the non-surgical treatment group, 134 patients had a primary lesion in the right lung and 122 in the left lung.

In the surgical treatment group, 174 patients had adenocarcinomas, 45 had squamous cell carcinomas, 12 had adenosquamous cell carcinomas, and 6 had large-cell carcinomas. None of the patients in the surgical treatment group had a small-cell carcinoma. In the non-surgical

Table 2. Correlation between clinicopathological features and treatment for lung cancer

	All patients (n=493)	
	Surgery (%) (n=237)	Non-surgery (%) (n=256)
Age, median (range)	69 (37-87)	72 (31-95)
Gender		
male	139 (58.6)	189 (73.8)
female	98 (41.4)	67 (26.2)
Side of primary lesion		
Right lung	131 (55.3)	134 (52.3)
Left lung	106 (44.7)	122 (47.7)
Histologic Type		
Adeno carcinoma	174 (73.4)	144 (56.2)
Squamous cell	45 (19.0)	59 (22.8)
Adenosquamous	12 (5.1)	0 (0.0)
Large cell	6 (2.5)	1 (0.4)
Small cell	0 (0.0)	52 (20.6)
Driver Mutation		
EGFR	66 (27.8)	44 (17.2)
EML4-ALK	3 (1.3)	3 (1.2)
Crinical / Pathologic Stage		
IA	129 (54.4)	3 (1.2)
IB	47 (19.8)	1 (0.4)
IIA	23 (9.7)	4 (1.6)
IIB	12 (5.1)	1 (0.4)
IIIA	26 (11.0)	17 (6.6)
IIIB	0 (0.0)	31 (12.1)
IV	0 (0.0)	199 (77.7)

treatment group, 144 patients had adenocarcinomas, 59 had squamous cell carcinomas, 1 had a large-cell carcinoma, and 52 had small-cell carcinomas. None of the patients in the non-surgical treatment group had an adenosquamous cell carcinoma. Thus, patients with adenosquamous cell carcinoma were diagnosed only by surgery.

In the surgical and non-surgical treatment groups, 54 and 44 patients had *EGFR* mutations, respectively, and 3 from each group had *EML4-ALK* fusion genes.

We measured pathological stage after surgery in the surgical treatment group : 129 patients were stage IA, 47 were stage IB, 23 were stage IIA, 12 were stage IIB, and 26 were stage IIIA. We also measured the clinical stage prior to non-surgical treatment : 3 patients were stage IA, 1 was stage IB, 4 were stage IIA, 1 was stage IIB, 17 were stage IIIA, and 31 were stage IV.

We also measured overall survival according to treatment group (Fig. 2). The patients who underwent surgery showed significantly longer overall survival than those who received non-surgical treatments (p<0.001, HR=0.084, 95% CI=0.059-0.119). In the surgical treatment group, the 5-year survival rate was 66.5%, but the median survival time had not yet been reached. In the non-surgical treatment group, the median survival time was 14 months.

We also categorized patients by histological type and assessed which anticancer drugs each patient had been

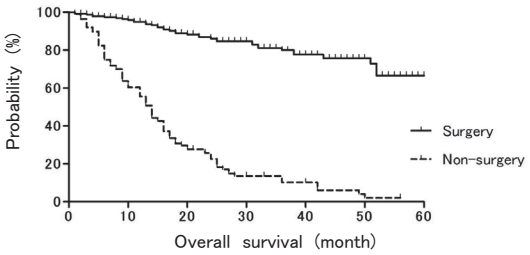

Fig. 2 Kaplan-Meier estimates of survival by treatment. The median duration of survival for the group non-surgery was 14 months. Corresponding to a hazard ratio for death of 0.084 ($p<0.0001$).

administered for first-line chemotherapy listed in Table 3. Among patients with adenocarcinomas, 3 were treated with carboplatin, paclitaxel, and bevacizumab ; 13 with cisplatin and pemetrexed ; 15 with carboplatin and pemetrexed ; 1 with carboplatin and paclitaxel ; 10 with cisplatin and docetaxel ; and 5 with gemcitabine. Gefitinib was used in 41 patients with adenocarcinomas who had *EGFR* mutations, and crizotinib was used in 3 patients with *EML4-ALK* fusion genes. All patients with driver mutations were treated with targeted therapy as first-line chemotherapy. The overall survival of the patients who received gefitinib was 19 months. Six patients were treated with radiotherapy alone, and 37 patients chose best supportive care. In patients with squamous cell carcinomas, 18 were treated with carboplatin and paclitaxel, 4 with cisplatin and docetaxel, 2 with carboplatin and gemcitabine, 12 with radiotherapy alone, and 21 with best supportive care. In patients with small-cell carcinomas, 12 were treated with cisplatin and etoposide, 11 with carboplatin and etoposide, 8 with cisplatin and irinotecan, 9 with carboplatin and irinotecan, 3 with radiotherapy alone, and 21 with best supportive care.

Discussion

Recently, the number of lung cancer patients has increased, and lung cancer has become the most common cause of death in Japan[2]. This increase has led to improvements in diagnostic methods and chemotherapeutic regimens for lung cancer.

A previous study reported that 437 patients were diagnosed with lung cancer in Akita Prefecture in 2002. Of

Table 3. Correlation between non-surgical treatment and histlogical type

Adenocarcinoma $n=144$ (%)		**Small Cell Carcinoma** $n=52$ (%)	
CBDCA + PAC + BEV	3 (2.1)	CDDP + VP-16	12 (23.1)
CDDP + PEM	13 (9.0)	CBDCA + VP-16	11 (21.2)
CBDCA + PEM	15 (10.5)	CDDP + CPT-11	8 (15.4)
CBDCA + PAC	1 (0.7)	CBDCA + CPT-11	9 (17.3)
CDDP + DTX	10 (7.0)	CPT-11	2 (3.8)
CBDCA + GEM	5 (3.5)	Radiotherapy	3 (5.7)
Gefitinib	41 (28.5)	BSC	7 (13.5)
Crizotinib	3 (2.1)		
Others	9 (6.3)	**Squamous Cell Carcinoma** $n=59$ (%)	
Radiotherapy	6 (4.2)	CBDCA + PAC	18 (30.5)
BSC	37 (26.1)	CDDP + DTX	4 (6.8)
		CBDCA + GEM	2 (3.4)
Large Cell Carcinoma $n=1$ (%)		Others	2 (3.4)
CDDP + DTX	1 (100)	Radiotherapy	12 (13.6)
		BSC	21 (42.3)

CDDP Cisplatin, *CBDCA* Carboplatin, *VP-16* Etoposide, *CPT-11* Irinotecan
PAC Paclitaxel, *DTX* Docetaxel, *PEM* Pemetrexed, *BEV* Bevacizumab, *GEM* Gemcitabine
BSC Best Supportive Care

these patients, 35% received surgical treatment and 65% received chemotherapy and/or radiotherapy[7]. In our study, 46% of the patients received surgical treatment. Thus, the proportion of patients who underwent surgical resection was increased compared with the previous report. In 2002, according to the same report, 42% of patients with lung cancer were classified as having stage I, II, or IIIA disease[7].

The number of early-stage patients was increased compared with the 2002 report. One factor contributing to this is improvements in CT technology, which today provides highly detailed, abnormal shadows, allowing for early detection. When we observe abnormal shadows, particularly ground-glass opacities (GGOs), we follow up with reference to the guidelines for the management of pulmonary nodules every few months[8]. Those guidelines state that any pulmonary nodules greater than 5 mm detected on the first CT scans should be classified as solid, part-solid, or pure ground-glass nodules (GGNs). It is recommended that a definite diagnosis be made when a solid nodule measures more than 10 mm in maximal diameter on a CT scan. When the maximal diameter of a solid nodule on CT is in the >5- but <10-mm range and the patient is a smoker, follow-up CT examinations are performed after 3, 6, 12, 18, and 24 months. If the patient is a non-smoker, follow-up CT examinations are performed at 4, 12, and 24 months[8]. The reason for the different follow-up examination intervals between smokers and non-smokers is that the lung cancer doubling time is shorter in smokers[9]. Part-solid nodules have a high probability of becoming malignant tumors[10]. However, inflammatory lesions also look like part-solid nodules ; therefore, CT is performed 3 months later to exclude inflammatory lesions. If a pure GGN is 15 mm or larger in maximal diameter on CT scans, then a definitive diagnosis should be made. If a pure GGN is less than 15 mm in maximal diameter, follow-up CT is performed at 3, 12, and 24 months[8].

The Japanese Lung Cancer Society recommends surgical treatment for patients in clinical stages I, II, and/or IIIA[5]. The 5-year survival rate for patients with lung cancer undergoing surgical treatment was 66.5% in this study. In general, in lung cancer cases undergoing surgery in Japan, the percentages of female patients, adenocarcinomas, small tumors, and aged patients have increased, whereas the rate of surgery-related deaths has decreased. With such changes, the 5-year survival rate for all lung cancer patients who underwent surgery was 69.6% in 2004[11]. Moreover, the 5-year survival rates were : stage IA, 82.0% ; stage IB, 66.1% ; stage IIA, 54.5% ; and stage IIB, 46.1%[11]. In our study, the 5-year survival rates were : stage IA, 81.2% ; stage IB, 56.6% ; stage IIA, 35.4% ; and stage IIB, 20.8%. The reason for the slightly lower (~3%) 5-year survival rate in this study may be the high number of elderly subjects. The Japanese lung cancer registry study contained 11,663 patients, whose mean age was 66.7 years[11]. In our study, the median age of the 237 patients who underwent surgical treatment was 68.5 years. A previous study suggested that the 5-year survival rate for older patients was worse than that for younger patients[12]. However, it was also reported that the 5-year survival rate for elderly patients has improved in general[13]. It seems likely that the number of elderly lung cancer patients will continue to increase in the future. We must adapt our surgical approach for elderly people and provide careful follow-up treatment.

From 2009 to 2013, 256 patients received non-surgical therapy ; of these, 65 received palliative therapy only and 191 received chemotherapy and/or radiotherapy. It is recommended that a treatment strategy be selected with regard to the ECOG-PS, patient age and histologic type of disease[5]. Among patients with a PS of 0 or 1, the treatment strategy was different for those patients 75 years old or older. Patients with a PS of 2 often received chemotherapy with a single agent. Patients with a PS of 3 or 4 received best supportive care. However, the applied treatment strategy was different for patients with a driver mutation. Patients with an adenocarcinoma and an *EGFR* mutation who were classified as ECOG-PS 3 or 4 received targeted molecular therapy[14]. However, careful follow up is necessary to prevent the onset of side effects for cases with a poor PS[15,16].

All patients diagnosed at our hospital were examined for genetic mutations. For all lung cancer patients with *EGFR* mutations, we used *EGFR* tyrosine kinase inhibitors (EGFR-TKIs) as first-line chemotherapy in our hospital from 2009 to 2013. PFS can be extended by the

use of EGFR-TKIs during primary therapy[17]. However, in deciding when to use EGFR-TKIs for patient treatment, there is some discussion about whether combination therapy with chemotherapy and EGFR-TKIs or monotherapy with an EGFR-TKI is more appropriate. In the NEJ005 clinical trial, the North East Japan Study Group examined whether concurrent or sequential therapy with chemotherapy and an EGFR-TKI was more effective. Presently, combination therapy with chemotherapy and an EGFR-TKI and monotherapy with an EGFR-TKI are being examined in the NEJ009 clinical trial.

In recent years, tumor angiogenesis has come to be viewed as important in lung cancer proliferation and metastasis[18]. Overall survival is extended when an angiogenesis inhibitor is combined with conventional chemotherapy[19]. The most common chemotherapeutic regimens for adenocarcinomas include pemetrexed. Recently, maintenance therapy using pemetrexed has been recommended. Paz-Arez et al.[20] showed that overall survival was extended in patients receiving maintenance therapy. However, no clear policy has yet been made in our hospital as to whether maintenance therapy should be provided or whether angiogenesis inhibitors should be used.

It is recommended to select a treatment strategy with regard to the patient's ECOG-PS, age and smoking history[5]. Because we referred to past hospitalization medical records in this study, we did not examine the ECOG-PS or smoking history of the patients, which is a limitation of our study. It is necessary for us to reach a clear policy on drug regimens for lung cancer patients with reference to objective factors, including the ECOG-PS, age, histological type of disease, mutations and smoking history.

Conclusions

In conclusion, 493 patients (328 men and 165 women, median age=70 years) with lung cancer were enrolled in this study from 2009 to 2013. Those patients who underwent surgical treatment showed significantly longer overall survival than those who received non-surgical treatment. Indeed, their 5-year survival rate was 66.5%. In total, 255 patients received non-surgical treatment. However, the reasoning behind the chemotherapy treatment strategy decisions was unclear. We must develop a clear treatment strategy with regard to various objective factors, including the ECOG-PS and age of the patient.

References

1) Health, Labour and Welfare Statistics Association, Japan. *Journal of health and welfare statistics 2013.*
2) *Annual Health Statistics of Akita 2013.*
3) Gridelli, C., Rossi, A. and Maione, P. (2003) Treatment of non small cell lung cancer state of the art and development of new biologic agent. *Oncogene,* **22**, 6629-6638.
4) Yatabe, Y. (2013) Recent changes in the therapeutic strategy for NSCLC in association with new anticancer agents. *Rinsho Byori,* **61**, 328-333.
5) The Japan Lung Cancer Society, *Medical guidelines for lung cancer 2012.*
6) Mitsudomi, T. (2013) Driver gene mutation and target therapy of lung cancer. *Jpn. J. Cancer Chemother.,* **40**, 285-290.
7) Sasaki, M., Miura, M., Watarai, J., *et al*. (2006) A statistical analysis of lung cancer in Akita Prefecture in 2002. *Akita Med. J.,* **56**, 73-81.
8) The Japanese Society of CT Screening. (2013) *Guidelines for the management of pulmonary nodules detected by low-dose CT lung cancer screening version 3.*
9) Hasegawa, M., Sone, S., Takashima, S., Li, F., Yang, Z.G., Maruyama, Y. and Watanabe, T. (2000) Growth rate of small lung cancers detected on mass CT screening. *Brit. J. Radiol.,* **73**, 1252-1259.
10) Li, F., Sone, S., Abe, H., Macmahon, H. and Doi, K. (2004) Malignant versus benign nodules at CT screening for lung cancer : comparison of thin-section CT findings. *Radiology,* **233**, 793-798.
11) Sawabata, N., Miyaoka, E., Asamura, H., *et al*. (2011) Japanese lung cancer registry study of 11,663 surgical cases in 2004. *J. Thorac. Oncol.,* **6**, 1229-1235.
12) Asamura, H., Goya, T., Koshiishi, Y., *et al*. (2008) Japanese Joint Committee of lung cancer registry. A Japanese lung cancer registry study : prognosis of 13,010 resected lung cancers. *J. Thorac. Oncol.,* **3**,

46-52.

13) Koike, T., Yamato, Y., Asamura, H., *et al*. (2009) Improvements in surgical results for lung cancer from 1989 to 1999 in Japan. *J. Thorac. Oncol.,* **4**, 1364-1369.

14) Inoue, A., Kobayashi, K., Usui, K., *et al*. (2009) First-line gefitinib for patients with advance non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication chemotherapy. *J. Clin. Oncol.,* **271**, 394-400.

15) Ando, M., Okamoto, I., Yamamoto, N., *et al*. (2006) Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. *J. Clin. Ocol.,* **24**, 2549-2556.

16) Kudoh, S., Kato, H., Nishiwaki, Y., *et al*. (2008) Interstitial lung disease in Japanese patients with lung cancer : a cohort and nested case-control study. *Am. J. Respir. Crit. Care Med.,* **177**, 1348-1357.

17) Maemondo, M., Inoue, A., Kobayashi, K., *et al*. (2010) Gefitinib or chemotherapy for non-small cell lung cancer with mutated EGFR. *N. Engl. J. Med.,* **362**, 2380-2388.

18) Sandler, A (2007) Bevacizumab in non-small cell lung cancer. *Clin. Cancer Res.,* **13**, 4613-4616.

19) Sandler, A., Gray, R., Perry, MC., Brahmer, J., Schiller, JH., Dowlati, A., Lilenbaum, R. and Jounson, DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N. Engl. J. Med.,* **355**, 2542-2550.

20) Paz-Arez, L., de Marinis, F., Dediu M., *et al*. (2012) Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT) : a double-blind, phase 3, randomised controlled trial. *Lancet. Oncol.,* **13**, 247-255.