

Review Article

Cutting-edge Medical Treatment for Advanced Non-small Cell Lung Cancer

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Abstract

The advent of molecular targeted drugs and effective second-line treatment for inoperable, advanced, Non-Small Cell Lung Cancer (NSCLC) has rapidly improved treatment outcomes. Conventional first-line chemotherapy regimens included all NSCLC, with the same treatment methods for squamous cell and non-squamous cell carcinomas. In addition, second-line or later treatment was not very effective in improving prognosis. However, there has been a recent paradigm shift in treatment options for NSCLC. In other words, 1) age and Performance Status (PS), 2) presence or absence of co-existing disease, 3) first-line vs. second-line or later treatment, 4) gene profiling for Epidermal Growth Factor Receptor (EGFR) gene mutations, and 5) squamous cell carcinomas vs. non-squamous cell carcinomas have become important factors in selecting treatment regimens.

Recent advances in research have shown that the presence or absence of the Echinoderm Microtubule-associated protein-Like 4 (EML4) and Anaplastic Lymphoma Kinase (ALK) fusion gene is important genetic information when considering the use of ALK inhibitors. Previously, the same regimens were selected for NSCLC regardless of tissue type, but clinical trial results of new drugs like pemetrexed and bevacizumab have now shown that the optimal treatment method differs for squamous cell vs. non-squamous cell carcinomas. This paper presents an overview, based on the most up-to-date knowledge, on selecting treatment in lung cancer, particularly advanced NSCLC.

INTRODUCTION

Stage IV Non-Small Cell Lung Cancer (NSCLC) is currently not curable and is mainly treated with chemotherapy to prolong survival and improve Quality of Life (QOL). The indications for chemotherapy must be decided based on the patient's Performance Status (PS), organ function, co-existing diseases, and toxicity of each drug. With the recent advent of new drugs, treatment should now be selected based on molecular profiles, such as EGFR gene mutation and EML4-ALK fusion gene status, and on histological type (squamous vs. non-squamous cell carcinomas), and indeed, the Japan Lung Cancer Society guidelines now propose that the course of treatment should be selected accordingly in Japan, as shown in Figure 1.

First-line chemotherapy

A meta-analysis reported in 1995 comparing chemotherapy and Best Supportive Care (BSC) showed that the chemotherapy group (n = 416) had a 1.5-month longer median survival and a 10% improvement in 1-year survival compared to the BSC group (n = 416) [1]. Since then, patients with a good PS (\leq PS1)

have received two-drug, platinum-based regimens as standard treatment. On the basis of the results of the ECOG1594 clinical trial [2] in the United States and the Four-Arm Cooperative Study (FACS) [3] in Japan, patients with inoperable NSCLC (stage IIIB-IV, PS 0-1) receive cisplatin (CDDP) plus irinotecan, carboplatin plus paclitaxel, CDDP plus gemcitabine (GEM), or CDDP plus vinorelbine as standard treatment.

A) Pemetrexed (PEM; Alimta®, Eli-Lily): Efficacy of pemetrexed for induction therapy and maintenance therapy in non-squamous NSCLC

A phase III study compared CDDP plus GEM, a standard regimen for induction initial chemotherapy in advanced NSCLC, and CDDP plus pemetrexed in 1725 chemotherapy-naïve patients with stage IIIB/IV NSCLC and a PS of 0-1 [4]. For Overall Survival (OS) as the primary endpoint, non-inferiority of cisplatin/pemetrexed vs. cisplatin/gemcitabine was demonstrated (median survival: 10.3 months vs. 10.3 months, HR 0.94, 95% CI: 0.84-1.05).

Hemato-toxicity was significantly lower with cisplatin/

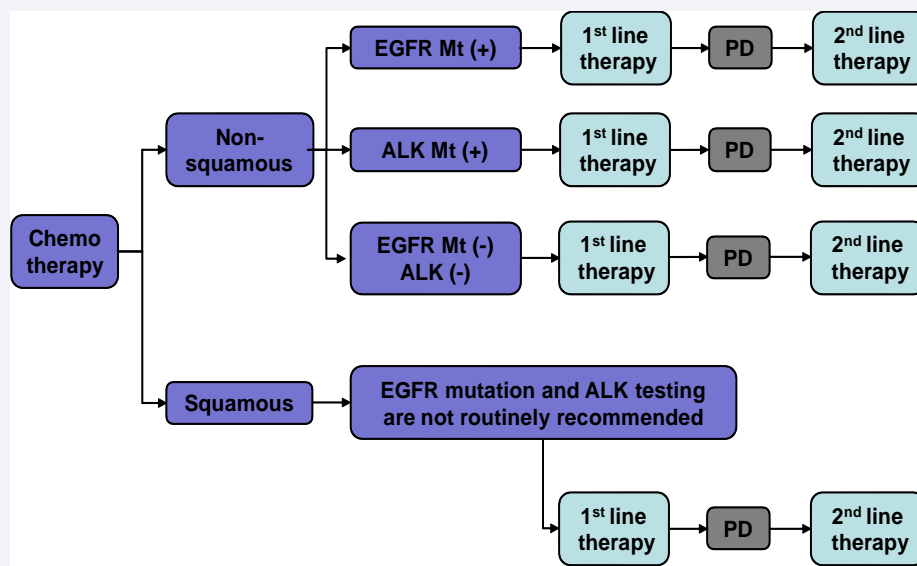


Figure 1 Systemic therapy in patients With Stage IV NSCLC according to the 2013 Lung Cancer Treatment Guidelines by The Japan Lung Cancer Society. **Abbreviations:** EGFR: Epidermal Growth Factor Receptor; ALK: Anaplastic Lymphoma Kinase; Mt: Mutated; PD: Progressive Disease.

pemetrexed than with cisplatin/gemcitabine.

That study focused on the results of a subset analysis by histological type. In squamous cell carcinomas (473 patients), cisplatin/pemetrexed was significantly inferior to cisplatin/gemcitabine in terms of overall survival (median survival: 9.4 months vs. 10.8 months, HR 1.23, 95% CI: 1.00-1.51). However, in non-squamous cell carcinomas (1000 patients), overall survival was significantly better with cisplatin/pemetrexed than with cisplatin/gemcitabine (median survival: 11.8 months vs. 10.4 months, HR 0.81, 95% CI: 0.70-0.94) (Figure 2). With regard to differences in the efficacy of pemetrexed based on histological type, when the results of several studies using pemetrexed alone were combined and analyzed, higher efficacy in non-squamous cell carcinomas was similarly found. Based on this evidence, CDDP plus pemetrexed is now used as a standard regimen for initial chemotherapy in advanced non-squamous NSCLC.

Platinum-based combinations for initial therapy in advanced NSCLC may be given for up to 4 to 6 cycles, provided that the condition does not worsen and that toxicity is tolerable. Clinical trial results to date have not shown any clinical benefit in continuing treatment beyond this time. However, with the advent of pemetrexed, which has relatively mild toxicity and can be given long term, pemetrexed alone for continuation maintenance therapy without a break-in treatment has been evaluated in patients in whom platinum-based combinations were successful as initial therapy.

After 4 cycles of cisplatin/pemetrexed in advanced non-squamous NSCLC (939 patients) in the PARAMOUNT Study, patients who achieved at least Stable Disease (SD) were randomized, and pemetrexed alone as continuation maintenance therapy (359 patients) was compared to placebo (180 patients). Progression-Free Survival (PFS) after randomization, which was the primary endpoint, was significantly longer in the maintenance pemetrexed group (median PFS: 3.9 months vs. 2.6 months,

HR 0.64, 95% CI: 0.51-0.81). In addition, overall survival was significantly improved in the maintenance pemetrexed group (13.9 months vs. 11.0 months, HR 0.78, 95% CI: 0.64-0.96) [5] (Figure 3).

Based on these results, the Lung Cancer Treatment Guidelines by the Japan Lung Cancer Society were revised in 2013, and the recommendation grade for pemetrexed maintenance therapy was increased from C1 to B. Platinum-based combination therapy with pemetrexed for advanced non-squamous cell carcinomas is now a commonly used regimen in Japan. In patients who achieve an antitumor response after four cycles and who can tolerate the toxicity, maintenance therapy with pemetrexed alone is a treatment option that should be considered.

B) Bevacizumab (Avastin® Roche): Efficacy of bevacizumab for induction therapy in non-squamous NSCLC.

Bevacizumab is a humanized monoclonal antibody that targets Vascular Endothelial Growth Factor (VEGF), inhibits angiogenesis, and reduces tumor growth and tumor survival. In the United States, a phase III study (E4599) in advanced NSCLC (excluding squamous cell carcinomas) evaluated the significance of adding bevacizumab (15 mg/kg) to combined chemotherapy with carboplatin (AUC 6) and paclitaxel (200 mg/m²), which was used as standard treatment. Overall survival, which was the primary endpoint, was significantly prolonged (median survival: 12.3 months vs. 10.3 months, HR 0.79, p=0.003) [6]. In addition, PFS (6.2 months vs. 4.5 months) and the overall response rate (35% vs. 15%) were significantly improved.

In Japan, a randomized phase II study evaluated the efficacy and safety of adding bevacizumab (15 mg/kg) to carboplatin (AUC 6)/paclitaxel (200 mg/m²), with 121 patients in the bevacizumab combination group and 59 patients in the chemotherapy alone group. Among 175 patients in whom efficacy was analyzed, the response rates were 60.7% in the bevacizumab combination group and 31.0% in the chemotherapy alone group. Efficacy

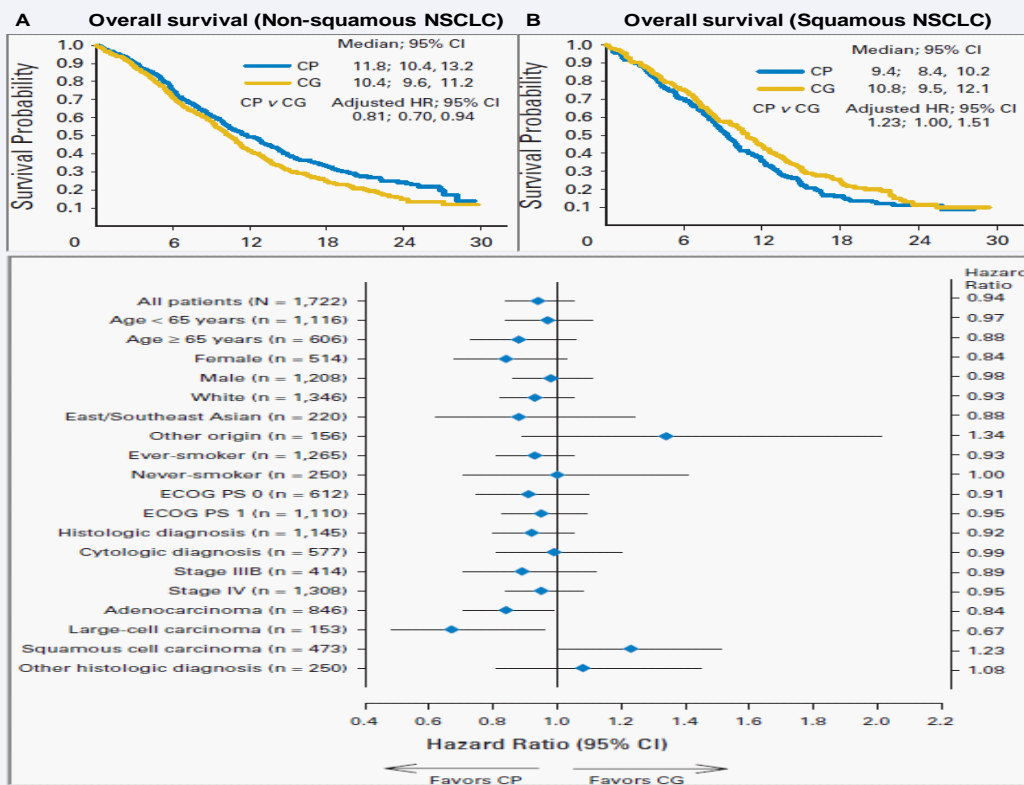


Figure 2 Survival hazard ratios (cisplatin/pemetrexed [CP] compared to cisplatin/gemcitabine [CG]) in groups according to baseline characteristics. (A) Significantly improved overall survival for cisplatin/pemetrexed compared with cisplatin/gemcitabine was observed in patients with non-squamous NSCLC. (B) Conversely, cisplatin/gemcitabine showed improved survival compared to cisplatin/pemetrexed in patients with squamous NSCLC. (C) Hazard ratios (HRs) and 95% confidence intervals (CIs) according to the subgroup analyses [4].

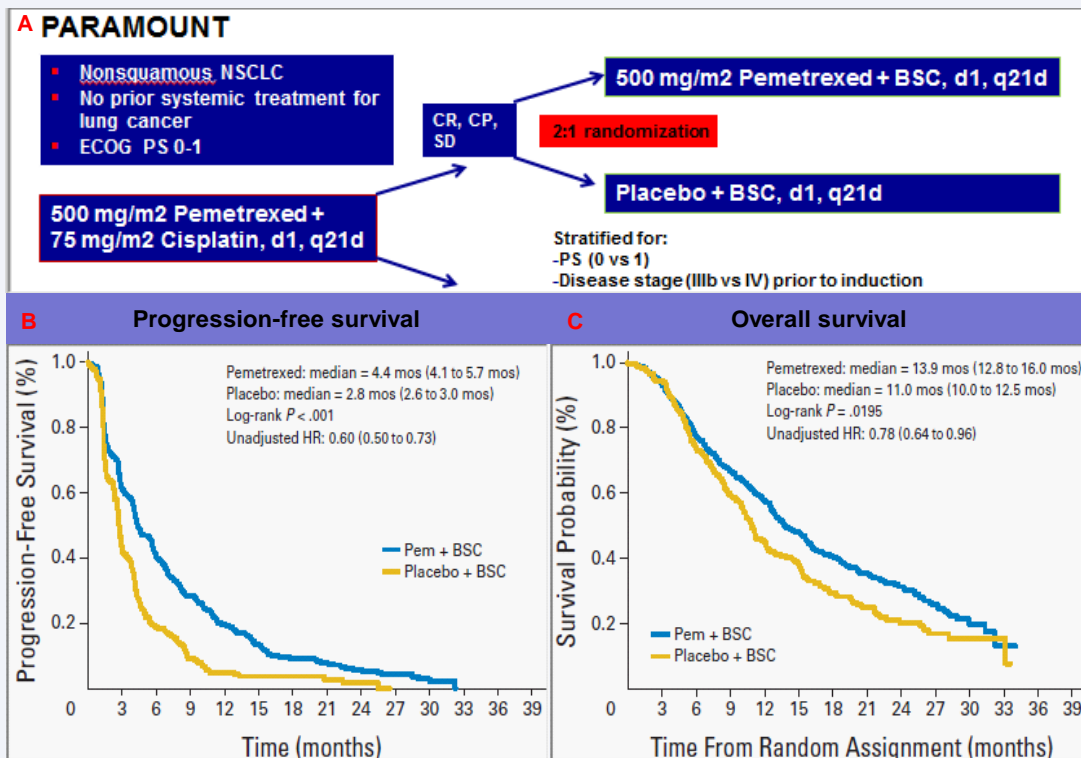


Figure 3 Continuation maintenance trial with pemetrexed [5].

was significantly better in the bevacizumab combination group ($p=0.0013$). The primary endpoint was PFS. The median PFS was 6.9 months in the bevacizumab combination group and 5.9 months in the chemotherapy alone group. PFS was significantly improved in the bevacizumab combination group (HR 0.61, 95% CI: 0.42-0.89, $p=0.009$) [7]. The results of adding bevacizumab to carboplatin/paclitaxel in Japanese patients with NSCLC (excluding squamous cell carcinomas) were consistent with the ECOG 4599 study results in the United States. This is an effective regimen for initial chemotherapy in patients with non-squamous cell advanced NSCLC.

In addition, the AVAiL trial [8] was a Randomized, Controlled Trial (RCT) to evaluate the efficacy of bevacizumab in lung cancer. This was a phase III study in which bevacizumab was added to CDDP + GEM. The primary endpoint of PFS was prolonged, thus demonstrating the superiority of adding bevacizumab.

The above results suggest that these regimens with the addition of bevacizumab may now be considered standard treatment (Figure 4). However, because of the high risk of hemoptysis in squamous cell carcinoma, this regimen is indicated in non-squamous cell carcinomas. Furthermore, in patients with tumor invasion of large blood vessels or who have cavitory lesions, this regimen should be administered cautiously, or is even generally contraindicated. Caution is also advised if hypertension or proteinuria develops during treatment. Because of concern about cerebral hemorrhage in patients with brain metastases, this regimen is "generally contraindicated," but based on the results of an overseas clinical trial [9] in patients with brain metastases, this was revised to "administer with caution" in June 2012.

C) EGFR-TKI (EGFR, epidermal growth factor receptor-TKIs, tyrosine kinase inhibitors) (Gefitinib: Iressa® AstraZeneca, Erlotinib: Tarceva® Roche Afatinib: Giotrif®, Gilotrif® Boehringer-Ingelheim)

Efficacy of EGFR-tyrosine kinase inhibitors (EGFR-TKIs) in EGFR gene mutation-positive NSCLC

Gefitinib and erlotinib are drugs that inhibit tyrosine kinase activity, which is important in EGFR signal transduction, and they are called EGFR-Tyrosine Kinase Inhibitors (EGFR-TKIs). These are the first molecular targeted drugs used in advanced NSCLC. Responders and non-responders to treatment with these drugs were identified, and a subsequent study showed that EGFR-TKIs were effective in patients with exon 19 deletions or exon 21 point mutations in the EGFR gene [10]. In addition, in patients with gene mutations in the EGFR tyrosine kinase domain, EGFR-TKIs exhibited dramatic antitumor activity not seen with previous anticancer drugs. Thus, gefitinib is considered useful as first-line treatment, as reported in the following three RCTs.

The iPASS study was a clinical trial conducted in Asia, where there is a high rate of EGFR gene mutation-positive NSCLC. Asian patients with adenocarcinoma who were nonsmokers or light smokers were randomly assigned to either gefitinib or CBDCA/paclitaxel as first-line chemotherapy. The primary endpoint in this RCT was PFS [11]. The results showed that gefitinib was superior in patients overall and in the group that was EGFR gene mutation-positive (Figure 5).

In Japan, before the rest of the world, a randomized phase III study was conducted in EGFR gene mutation-positive advanced NSCLC patients who had not previously received chemotherapy to compare the efficacy of platinum-based chemotherapy, which had been conventional standard treatment, with gefitinib alone. In the NEJ002 study [12] conducted by the North East Japan (NEJ) Study Group, 230 patients with EGFR gene mutation-positive advanced NSCLC who had not previously received chemotherapy were randomized to treatment with carboplatin/paclitaxel or gefitinib alone. Median PFS was 5.4 months in the chemotherapy group vs. 10.8 months in the gefitinib group, thus demonstrating superiority in the gefitinib group (HR: 0.30, 95% CI: 0.22-0.41, $p<0.001$). Gefitinib was also superior in terms of QOL [12].

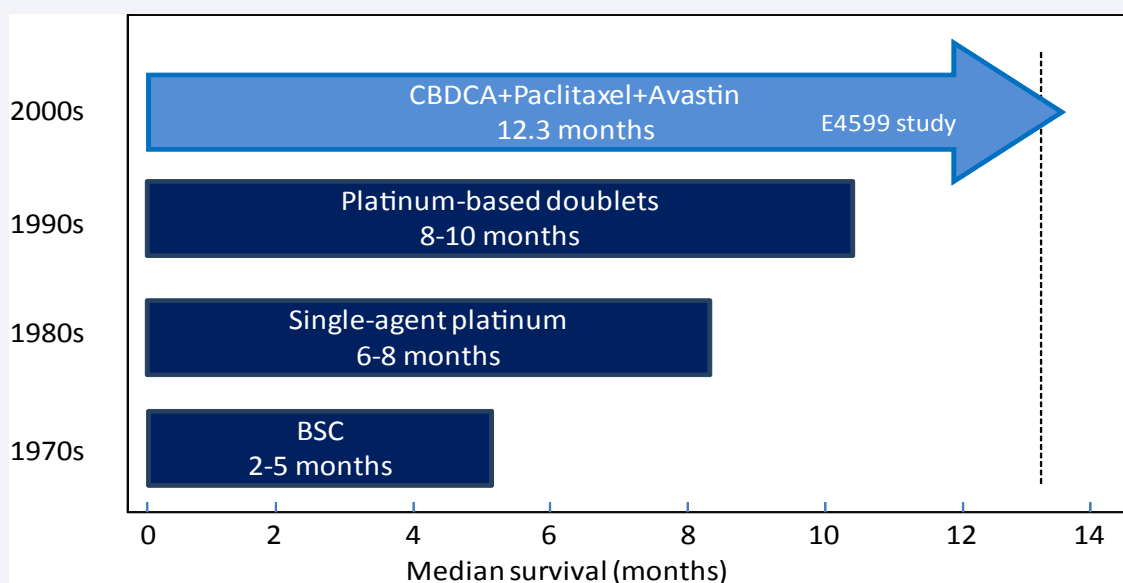


Figure 4 Comparison of survival times for current and previous treatment regimens in advanced non-squamous NSCLC. As shown in the E4599 study, adding bevacizumab (Avastin) to CBDCA/paclitaxel significantly prolongs survival compared to CBDCA/paclitaxel. BSC: Best Supportive Care; CBDCA: Carboplatin.

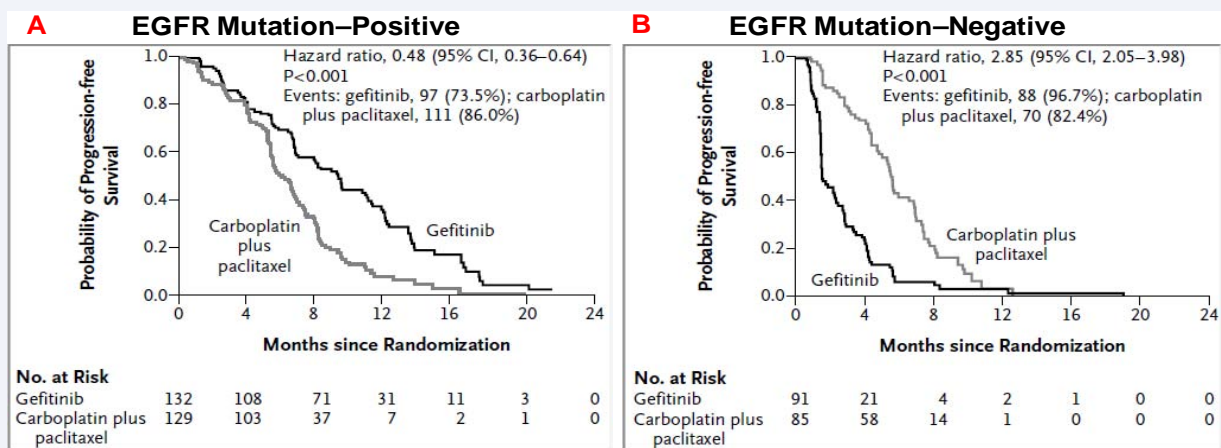


Figure 5 Kaplan-Meier curves for progression-free survival for (A) patients positive for the EGFR mutation and (B) patients negative for the EGFR mutation.

In the subgroup of patients with EGFR mutations, patients treated with gefitinib, as compared with those treated with carboplatin-paclitaxel, and had a remarkably prolonged progression-free survival.

Conversely, in the subgroup of patients without EGFR mutations, progression-free survival was slightly better in patients treated with chemotherapy [11].

In the WJTOG3405 study [13] conducted by the West Japan Oncology Group, 177 patients were randomized to receive treatment with either CDDP plus docetaxel chemotherapy or gefitinib alone. The median PFS, the primary endpoint, was 6.3 months in the chemotherapy group compared to 9.2 months in the gefitinib group, again demonstrating the superiority of gefitinib [13].

Furthermore, in phase III studies conducted overseas comparing platinum-based therapy with erlotinib as initial therapy in patients who were EGFR gene mutation-positive (OPTIMAL [14] and EURTAC [15]), PFS was significantly better in the erlotinib group (Table 1).

On the basis of these clinical trial data, the Lung Cancer Treatment Guidelines by the Japan Lung Cancer Society recommend EGFR-TKI drugs alone as an option for initial therapy in EGFR gene mutation-positive advanced NSCLC (recommendation grade A). In November 2011, the Indications and Usage in the package insert for gefitinib were revised to “inoperable or recurrent EGFR gene mutation-positive NSCLC.” This essentially restricted the use of gefitinib to EGFR gene mutation-positive patients. In addition, with regard to erlotinib, after a clinical trial in Japan as induction therapy in EGFR gene mutation-positive advanced NSCLC, expanded indications were approved for induction therapy in EGFR gene mutation-positive patients in June 2013.

Mean survival is more than 24 months when EGFR-TKIs are used appropriately in EGFR gene mutation-positive NSCLC. This far exceeds previous survival times for this stage of lung cancer. Therefore, EGFR-TKIs should be administered early, without missing an opportunity, in this patient group.

In recent years, afatinib, a second-generation EGFR-TKI that selectively and irreversibly inhibits the ErbB family members EGFR, HER2, and HER4, has been developed, and its therapeutic effects are gaining attention.

EGFR-TKIs are molecularly targeted drugs that competitively

inhibit the binding of adenosine 3-phosphate to the tyrosine kinase portion located in the intracellular domain of EGFR. As opposed to first-generation EGFR-TKIs such as gefitinib and erlotinib, which bind to EGFR reversibly, afatinib has been demonstrated to allow blocking of the EGFR pathway permanently by irreversibly binding to EGFR. Moreover, afatinib may bring about superior efficacy by inhibiting a wider range of HER family receptors related to EGFR pathway signaling, including HER2 and HER4. Additionally, a clinical effect of afatinib is expected against the exon20T790M point mutation, a secondary mutation of EGFR that is responsible for the development of drug resistance in approximately half of the patients treated with first-generation EGFR-TKIs [16].

The results of a phase III trial (LUX-Lung3) that compared standard CDDP plus pemetrexed combination therapy (group PC) with daily administration of afatinib (group A) in patients with untreated EGFR-mutated lung adenocarcinomas were reported at the 2012 American Society of Clinical Oncology (ASCO) annual meeting. In short, PFS, the primary endpoint, was significantly prolonged in group A compared to group PC (11.1 vs. 6.9 months; HR: 0.58, 95% CI: 0.43–0.78, p = 0.0004). Similarly, the response rate was significantly improved in group A compared to group PC (56% vs. 23%; p < 0.0001). Furthermore, the onset of certain symptoms commonly accompanying lung cancer that can restrict the everyday life of patients, such as coughing and dyspnea, was delayed in group A. On the basis of these results, an application was submitted to the European Medicines Agency for sales approval of afatinib as a therapeutic agent for NSCLC in Europe, in September 2012 [17].

In Japan, similar significant PFS prolongation and good response rates on subgroup analyses of Japanese patients in the same trial were reported at the annual Japanese Society of Medical Oncology meeting in 2012 [18]. Further to these results, afatinib will likely soon represent an effective treatment option for specific patient groups with lung cancer in Japan as well.

Table 1: Effect of EGFR-TKIs for 1st-Line Treatment in EGFR Mt (+) NSCLC.

Country	Study % of EGFR mutation type	Treatment arm	ORR (%)	mPFS (mo)	MST (mo)				
Japan	NEJ002	Gefitinib	74	10.8	27.7				
	Del 19 : 51%								
	L858R : 43%								
Japan	Others : 6%	CBDCA/PTX	31	5.4	26.6				
	WJTOG3405								
	Del 19 : 51%								
Japan	L858R : 49%	CDDP/DOC	32	6.6	38.8				
	OPTIMAL					Erlotinib	83	13.7	22.7
L858R : 47%									
China	EURTAC	Erlotinib	58	9.7	19.3				
						Del 19 : 66%			
						L858R : 34%			
Spain	Platinum/DOC or GEM	15	5.2	19.5					

Abbreviations: EGFR: Epidermal Growth Factor; TKI: Tyrosine Kinase Inhibitor; CBDCA: Carboplatin; PTX: Paclitaxel; CDDP: Cisplatin; DOC: Docetaxel; GEM: Gemcitabine; ORR: Overall Response Rate; mPFS: Median Progression-Free Survival; MST: Median Survival Time; mo: Months

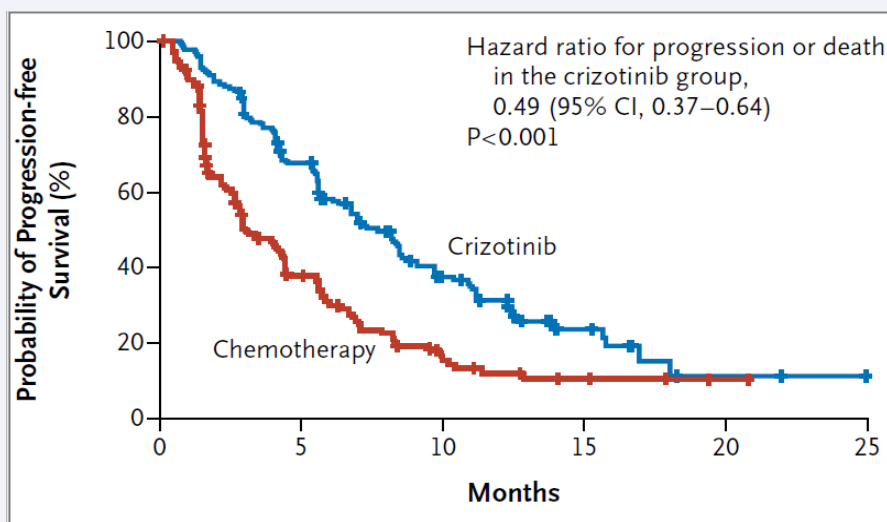


Figure 6 Phase III study of crizotinib versus pemetrexed or docetaxel in previously treated patients with advanced ALK-positive NSCLC.

The latest findings

In the latest European Society of Medical Oncology congress in 2012, good response rates and PFS prolongation regardless of the presence of the T790M point mutation were reported from a trial testing afatinib plus cetuximab (Erbix®) combination therapy for patients who developed resistance to first generation EGFR-TKIs. In addition, the disease control rate was also favorable (94%). When the participants were limited to patients enrolled from the beginning and treated for at least 6 months, the response rate was 40%, whereas the response rates were 38% and 47% in the T790M point mutation-positive and T790M point mutation-negative groups, respectively. The PFS and median holding time in this trial were 4.7 and 7.7 months, respectively. Hence, this therapy also appears promising as an alternative treatment regimen after acquisition of resistance to first-generation EGFR-TKIs [19].

D) ALK inhibitor (Crizotinib: XALKORI® Pfizer): Efficacy of crizotinib in EML4-ALK-positive NSCLC.

The dramatic clinical efficacy of EGFR-TKIs in EGFR gene mutation-positive NSCLC shows that when tumor growth is highly dependent (oncogenic addiction) on excessive growth signals due to a single molecular abnormality, as seen also in solid cancers, potent antitumor effects can be achieved by blocking the activity of that molecule. Identification of these molecular abnormalities is highly significant for molecular targeted treatment. From this perspective, the molecular target receiving the most attention for development of treatment in NSCLC is the EML4-ALK fusion gene, which was discovered by Mano and Soda et al. and reported in 2007 [20].

The EML4-ALK fusion gene is a very potent oncogene in which there is rearrangement and fusion of two genes, EML4

Table 2: Chemotherapy for Squamous NSCLC Lung Cancer Treatment Guidelines 2013 by the Japan Lung Cancer Society.

CDDP Regimen			CBDCA Regimen		
CDDP	75 mg/m ² , day 1		CBDCA	(AUC = 6), day 1	
PEM	500 mg/m ² , day 1	q3w	PTX	200 mg/m ² , day 1	q3w
CDDP	80 mg/m ² , day 1		CBDCA	(AUC = 5), day 1	
DOC	60 mg/m ² , day 1	q3w	GEM	1000 mg/m ² , days 1, 8	q3w
CDDP	80 mg/m ² , day 1		CBDCA	(AUC = 5), day 1	
GEM	1000 mg/m ² , days 1, 8	q3w	S-1	40 mg/m ² , bid, days 1-14	q3w
CDDP	80 mg/m ² , day 1				
VNR	25 mg/m ² , days 1, 8	q3w			
CDDP	80 mg/m ² , day 1				
CPT-11	60 mg/m ² , days 1, 8, 15	q4w			
CDDP	60 mg/m ² , day 8				
S-1	40 mg/m ² , bid days 1-21	q4-5w			

Abbreviations: CBDCA: Carboplatin; PTX: Paclitaxel; CDDP: Cisplatin; GEM: Gemcitabine; VNR: Vinorelbine; CPT-11: irinotecan.

and ALK, on the short arm of chromosome 2. The EML4-ALK fusion gene is present in 3-5% of patients with NSCLC; it is more common in younger patients (age ≤50 years), non/light smokers, and adenocarcinoma (signet ring cells are characteristic); it is exclusive to EGFR gene mutations, and its frequency does not vary greatly among ethnic groups.

A phase I study of crizotinib, an ALK tyrosine kinase inhibitor, was started in 2006. During this study, dramatic effects were observed in patients with EML4-ALK-positive NSCLC. Therefore, in an expanded cohort study in the same trial, the effects of crizotinib were investigated in ALK fusion gene-positive NSCLC. Crizotinib 250 mg twice daily was given to 149 patients, and a dramatic antitumor effect was confirmed, with a response rate of 60.8% and PFS of 9.7 months [21]. In August 2011, the US FDA approved crizotinib, without waiting for the results of a phase III study, for the treatment of EML4-ALK-positive NSCLC. Approval was granted in Japan in March 2012.

In an international, cooperative, randomized, phase III study, in which Japan also participated, to compare crizotinib as second-line treatment with chemotherapy (docetaxel or pemetrexed alone), PFS (7.7 months vs. 3.0 months, $p < 0.0001$) and the response rate (65.3% vs. 19.5%, $p < 0.0001$) were significantly better [22] (Figure 6). This established crizotinib as standard treatment in this patient group. In addition, a randomized phase III study is currently being conducted in previously untreated patients to compare combined cisplatin (or carboplatin)/pemetrexed with crizotinib. The effectiveness of crizotinib as induction therapy is also being evaluated.

2. Drug Treatment in advanced Squamous NSCLC: Molecular abnormalities that affect treatment selection in squamous NSCLC have not been found, and new molecular targeted drugs have not been introduced. Platinum-based combination chemotherapy is usually selected as the initial therapy in advanced cases. Table 2 shows some specific regimens (note: regimens that include pemetrexed are not used in squamous cell lung cancer). In actual clinical practice, factors considered when selecting these treatment regimens include differences in their toxicity profiles, their ease of administration, their cost,

and their availability at each medical institution. Carboplatin is superior to cisplatin in terms of milder GI toxicity (nausea/vomiting), no need to give large amounts of fluid to prevent renal dysfunction, and more convenient administration in outpatient settings. Efficacy of maintenance therapy in squamous NSCLC has not been demonstrated. These platinum-based combination regimens are repeated for up to six courses depending on their toxicity and effectiveness.

S-1 is a pyrimidine fluoride antineoplastic drug in which tegafur, a prodrug of 5-fluorouracil (5-FU), is compounded with gimeracil, which inhibits Dihydropyrimidine Dehydrogenase (DPD), an enzyme that degrades 5-FU, and oteracil potassium, a phosphorylation inhibitor, which reduces gastrointestinal toxicities such as diarrhea. Although 5-FU in itself has low efficacy for lung cancer, which has high DPD activity and thus leads to degradation of 5-FU, S-1 compounded with gimeracil is expected to exert a clinical effect on lung cancer. Indeed, a phase III trial (the LETS study) combining carboplatin was conducted to prove the non-inferiority of carboplatin plus oral S-1 therapy (group SC) compared to carboplatin plus paclitaxel therapy (group PC) in terms of OS in patients with NSCLC. In subgroup analysis according to histologic type, the median OS for squamous cell carcinoma were 14.0 and 10.6 months in group SC and group PC, respectively, with the S-1 group showing better outcomes [23] (Figure 7).

Moreover, in a phase III non-inferiority trial combining CDDP (CATSTRIAL) reported at the 2012 ASCO annual meeting, the efficacy and safety of S-1 plus CDDP (group SP) were verified by administering docetaxel plus CDDP (group DP) in the control arm. OS times, the primary endpoint, were 16.1 and 17.1 months in group SP and group DP, respectively (HR: 1.013, 96.4% CI: 0.837–1.227), whereas the PFS times were 4.9 and 5.2 months in group SP and group DP, respectively, thus demonstrating the non-inferiority of S-1 plus CDDP [24].

3. Second-line Treatment of advanced NSCLC: Patients with advanced NSCLC who are treated with first-line treatment will eventually have a recurrence. If their general condition is satisfactory at the time of recurrence, second-line treatment may be considered.

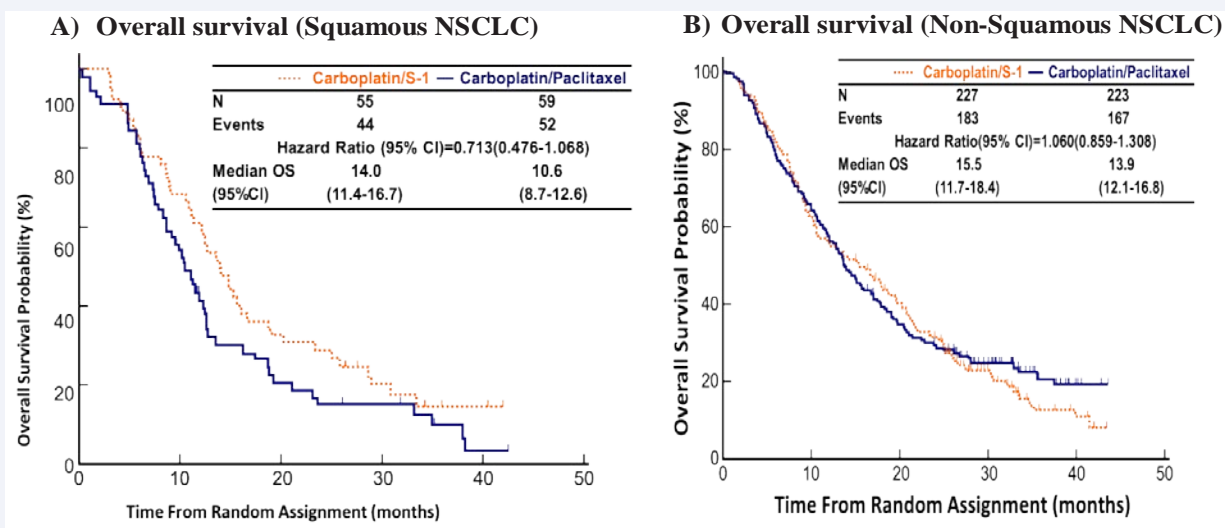


Figure 7 Results of the LETS Study WJTOG3605; a randomized, controlled, phase III clinical trial comparing carboplatin/TS-1 combination therapy with carboplatin/paclitaxel combination therapy for untreated stage IIIB/IV non-small cell lung cancer [23]].

A) EGFR-TKI: In EGFR gene mutation-positive patients who have not received an EGFR-TKI as initial therapy, the administration of gefitinib or erlotinib, which can achieve high response rates (about 70%), is actively being investigated.

An RCT (ISEL study) [25] compared gefitinib and Best Supportive Care (BSC) in patients with NSCLC who were refractory or had recurrences after platinum-based chemotherapy. The results showed that gefitinib was not superior in the overall population. However, a subanalysis in populations with higher EGFR gene mutation rates, including Asians, non-smokers, females, and patients with adenocarcinoma, showed that gefitinib was more effective than BSC. Based on these results, gefitinib was no longer used in actual clinical practice with these patients in Western countries, but in Japan, gefitinib is frequently used as standard second-line treatment in EGFR gene mutation-positive patients.

Meanwhile, a similar clinical trial (BR21) [26] with erlotinib was also conducted. The results showed that unlike gefitinib, erlotinib did prolong PFS compared to BSC alone in the overall population. Based on these results, erlotinib was established as standard second-line treatment in Western countries. A subset analysis in BR21 suggested that erlotinib may also be effective in males and in patients without EGFR gene mutations. Similarly, in patients who are EML4-ALK fusion gene-positive and have not received an ALK inhibitor, crizotinib should be considered.

Docetaxel:DOC:Taxotere ®; Aventis, Pemetrexed: PEM: Alimta®, Eli-Lily: Phase III studies in NSCLC that is refractory to, or that recurs after responding to, platinum-based combinations have shown that docetaxel and pemetrexed prolong survival compared to BSC and may be treatment options. Docetaxel (60 mg/m² every 3 weeks) was reported to significantly prolong survival compared to BSC. This established docetaxel monotherapy as standard second-line treatment [27].

A phase III study failed to show that pemetrexed (500 mg/m² every 3 weeks) was non-inferior to docetaxel, but therapeutic efficacy was nearly similar to docetaxel, and toxicity was milder.

Therefore, in non-squamous cell lung cancer in which pemetrexed has not been used as the initial therapy, its use as second-line or later treatment is actively being investigated [28].

CONCLUSION

Recent research advances have shown that optimal treatment selection in advanced NSCLC differs according to gene profiles such as EGFR gene mutations and whether the histology is squamous cell or non-squamous cell carcinoma. Treatment outcomes have improved dramatically in patients with NSCLC who are EGFR gene mutation-positive or EML4-ALK fusion gene-positive. Therefore, evaluation of these tumor gene profiles before starting treatment is essential.

On the other hand, in small cell lung cancers, effective molecular targeted drugs and other new anticancer drugs to markedly prolong survival have not yet been discovered. Hopefully, new drugs can be developed for these lung cancer histologic types.

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