Table 3. Randomized Phase III Trial of Platinum Doublet ± EGFR-TKI

Trials	n		Response Rat (%)	TTP (M)	MST (M)	p Value
INTACT-1	1,093	GP + gefitinib (500mg)	49.7	5.5	9.9	NS
		GP + gefitinib (250mg)	50.3	5.8	9.9	
		GP + placebo	44.8	6.0	10.9	
INTACT-2	1,037	PC + gefitinib (500mg)	30.0	4.6	8.7	NS
		PC + gefitinib (250mg)	30.4	5.3	9.8	
		PC + placebo	28.7	5.0	9.9	
TRIBUTE	1,059	PC + erlotinib (150mg)	21.5	5.1	10.6	NS
		PC + placebo	19.3	4.9	10.5	
TALENT	1,172	GP + erlotinib (150mg)	31.5	5.9	10.8	NS
		GP + placebo	29.9	6.2	11.0	

GP : GEM + CDDP, PC : PTX + CBDCA

EGFR-TKI: Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor

TTP: Time To Progression

MST: Median Survival Time

M: Month

NS: Not Significant

GEM: Gemcitabine

CDDP: Cisplatin

PTX: Paclitaxel

CBDCA: Carboplatin

M (50, 51). For the treatment of such resistant cases, an irreversible EGFR inhibitor has been developed and clinical trials are now under way (52).

6) Anti-EGFR antibodies

Antibodies directed against EGFR that are used for therapy include cetuximab (a chimeric IgG1 antibody), matuzumab (a humanized IgG1 antibody), panitumumab (a completely humanized IgG2 antibody), etc. Clinical trials of these agents are now under way in patients with various cancers.

a. Cetuximab

A phase II clinical study of cetuximab monotherapy in previously treated cases of NSCLC yielded a response rate of 4.5%. Toxicity was mild, but skin eruptions were seen in about 90% of all patients (grade 3/4 in 6.1%) (53).

A randomized phase II clinical study designed to evaluate the effects of the addition of cetuximab to CDDP + vinorelbine (VNR) therapy in 86 previously treated cases of NSCLC has been reported. The response rate, mPFS and MST were 35%, 5.0 months and 8.3 months, respectively, in the CDDP + VNR + cetuximab group, while they are 28%, 4.6 months and 7.3 months, respectively, in the CDDP + VNR group (54). In another randomized phase II clinical study (SWOG 0342) comparing a synchronous combined therapy (4 cycles of CBDCA + PTX therapy and simultaneously started cetuximab therapy for one-year) with a sequential combined therapy group (start of cetuximab therapy after completion of 4 cycles of CBDCA + PTX therapy), the response rate tended to be higher in the synchronous combined therapy group (34% vs. 31%), while a PFS of 4 months and MST of 11 months was obtained in both groups (55).

A randomized phase III clinical study (BMS 099) was carried out to compare CBDCA + taxane (PTX or DOC) therapy with CBDCA + taxane + cetuximab therapy in 676 previously untreated patients with NSCLC. The response rate was 17.2% in the CBDCA + taxane group and 25.7% in the CBDCA + taxane + cetuximab group, while no significant difference was noted in the primary endpoint, that is, PFS between the two groups (4.24 months vs. 4.40 months, p=0.2358) (56). Furthermore, a randomized phase III clinical study (FLEX) was carried out to compare CDDP + VNR therapy with CDDP + VNR + cetuximab therapy in 1,125 previously untreated patients with NSCLC showing positive EGFR expression. The response rate was significantly higher in the CDDP + VNR + cetuximab group (36%) than in the CDDP + VNR group (29%) (p=0.010). No significant difference in the PFS was observed between the two groups (mPFS: 4.8 months in both groups), however, the MST (a primary endpoint) was extended in the group additionally receiving cetuximab (10.1 months vs. 11.3 months, p=0.044) (57). In a subgroup analysis in the same study, the survival of Asian patients was poorer in the CDDP + VNR + cetuximab group (20.4 months vs. 17.6 months), probably because of the influence of EGFR-TKIs used for second-line and subsequent treatment.

Higher efficacy was obtained when cetuximab, an anti-EGFR antibody, was used in combination with chemotherapy than when it was used alone, unlike the findings ob-

Table 4. Clinical Trials of Cetuximab

Investigator	No of cases	Regimen	Response Rate (%)	PFS (M)	MST (M)	IHC
Rosell	44	CDDP + VNR	28	4.2	7.0	+
	43	CDDP + VNR + C225	35	4.8	8.3	+
Butts	66	Plat + GEM	18	4.2	9.3	—
	65	Plat + GEM + C225	28	5.1	12.0	—
Herbst	106	CBDCA + PTX + C225	34	4.0	11.0	—
	117	CBDCA + PTX⇒C225	31	4.0	11.0	—
Lynch	338	CBDCA + taxane	17	4.2	—	—
	338	CBDCA + taxane + C225	26	4.4	—	—
Pirker	568	CDDP + VNR	29	4.8	10.1	+
	557	CDDP + VNR + C225	36	4.8	11.3	+

PFS: Progression-Free Survival
MST: Median Survival Time
IHC : Immunohistochemistry
M : Month
CDDP: Cisplatin
PTX: Paclitaxel

tained for EGFR-TKIs (Table 4). A phase III clinical study designed to evaluate the effects of the addition of cetuximab to second-line chemotherapy (PEM or DOC) is now underway (58).

2. Anti-VEGF antibodies

1) Bevacizumab

Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). VEGF is not only involved in neovascularization, but also enhances the vascular permeability (59). Bevacizumab binds to VEGF to inhibit the binding of VEGF to VEGF-R, thereby also inhibiting vascularization. In addition, this drug reduces the interstitial pressure within tumor cells through normalizing tumor vessels, possibly leading to improved delivery of cytotoxic anticancer agents to tumor cells and manifestation of synergistic effects when this antibody is used in combination with chemotherapy (60).

The Eastern Cooperative Oncology Group (EOCG) carried out a randomized phase II clinical study to compare three groups of patients with advanced or recurrent NSCLC, i.e., the CBDCA + PTX (CP) therapy group (control arm), the CBDCA + PTX + bevacizumab 7.5 mg/kg group (CPB 7.5 group) and the CBDCA + PTX + bevacizumab 15 mg/kg group (CPB 15 group). The primary endpoint of progression-free survival was significantly longer in the CPB 15 group:* p=0.023 (control vs. CPB 7.5 group vs. CPB 15 group: 4.2 months* vs. 4.3 months vs. 7.4 months*), and the best response rate (18.8% vs. 28.1% vs. 31.5%) and overall survival (14.9 months vs. 11.6 months vs. 17.7 months) were also obtained in the CPB 15 group (61). However, severe hemoptysis was seen in 6 patients (9%) and 4 patients died following combined use of bevacizumab with chemotherapy. Squamous cell carcinoma, presence of tumor necrosis and a central location of the tumor were identified as the factors associated with severe hemoptysis. In a subsequent randomized phase III clinical study (ECOG 4599) designed to compare CBDCA + PTX (CP group) with CBDCA + PTX + bevacizumab 15 mg/kg (CPB group), patients with squamous cell carcinoma and patients who had hemoptysis or brain metastasis were excluded from the subject population to reduce the incidence of severe adverse events. In this study, significantly better outcomes were obtained in the CPB group in terms of the response rate (15% vs. 35%, p<0.001), PFS (mPFS: 4.5 months vs. 6.2 months, p<0.001) and overall survival (MST: 10.3 months vs. 12.3 months, p=0.003) (62). This was the first study to demonstrate prolongation of the survival period in patients with NSCLC following administration of a molecule-targeted drug in combination with chemotherapy. On the basis of the results of this study, CPB therapy was adopted by ECOG as the new standard therapy for non-squamous cell carcinoma. However, despite exclusion of patients who were at a high risk for hemoptysis from the subject population, the incidence of grade 3 or more severe bleeding was still significantly higher in the CPB group (0.7% vs. 4.4%, p<0.001) and 7 patients from the CPB group died of bleeding (5 deaths from hemoptysis and 2 deaths from gastrointestinal bleeding). The non-hematological toxicities (grade 3/4) observed at a high incidence were hypertension (5.6%), proteinuria (4.2%), malaise (5.1%), and dyspnea (5.6%).

The results of a randomized phase III clinical study (AVAiL) in which 1,043 patients with NSCLC (excluding squamous cell carcinoma) with no prior history of chemotherapy were divided into three treatment groups, i.e., the GEM + CDDP therapy group (GC group), GEM + CDDP +

bevacizumab 7.5 mg/kg therapy group (GCB 7.5 mg/kg group), and the GEM + CDDP + bevacizumab 15 mg/kg therapy group (GCB 15 mg/kg group). The primary endpoint, PFS, was extended significantly by the addition of bevacizumab to the therapy (mPFS: 6.2 months vs. 6.8 months vs. 6.6 months, p=0.0003*) and the response rate was also higher in the GCB groups (20.1% vs. 34.1% vs. 30.4%) (63). However, the MST did not differ significantly between any two of the three groups (13.1 months vs. 13.6 months vs. 13.4 months, p=0.42*) (*comparison between the GC group and GCB 7.5 mg/kg group) (64). The absence of significant inter-group differences in the overall survival period despite the finding of significant inter-group differences in the PFS was considered to be attributable to the chemotherapy administered for the second/subsequent-line treatment. During the ASCO meeting in 2009, the results of a randomized phase II clinical study in Japanese patients were reported. This study, which was designed to evaluate the safety and efficacy of two regimens (CPB vs. CP), similar to the evaluation in ECOG 4599, revealed favorable outcomes of CPB (65).

In addition, a study to evaluate the safety of initial treatment with a combination of standard chemotherapy and bevacizumab (7.5 or 15 mg/kg) was carried out (SAiL study) in 2,240 patients with advanced NSCLC. The incidence of severe adverse events associated with bevacizumab was 23.5%, however, the incidence of grade 3-5 bleeding in the central nervous system was 0.4% and that of hypertension was 0.7%. Thus, the therapy could be administered relatively safely (66).

A randomized phase II clinical study was carried out in patients with recurrent or therapy-resistant NSCLC (other than squamous cell carcinoma) allocated to one of the three following treatment arms, Arm 1: chemotherapy (DOC or pemetrexed [PEM]) + placebo, Arm 2: chemotherapy (DOC or PEM) + bevacizumab, and Arm 3: erlotinib + bevacizumab. The response rate, mPFS and MST were 12.2%, 3.0 months and 8.6 months, respectively, in Arm 1, 12.5%, 4.8 months and 12.6 months, respectively, in Arm 2, and 17.9%, 4.4 months and 13.7 months, respectively, in Arm 3. Thus, the regimens containing bevacizumab tended to yield better outcomes. The incidence of severe toxicities was the lowest in the erlotinib + bevacizumab group (67). On the basis of these results, a randomized phase III clinical study (BETA Lung) was carried out, comparing erlotinib + placebo therapy (E+P group) with erlotinib + bevacizumab therapy (E+B group) in 636 patients with recurrent NSCLC. The response rate (6.2% vs. 12.6%, p=0.006) and PFS (mPFS: 1.7 months vs. 3.4 months, p<0.0001) were significantly better in the E+B group, while the overall survival period (MST: 9.2 months vs. 9.3 months, p=0.7583) did not differ significantly between the two groups. As for the reason why the significant inter-group difference in the PFS was not reflected in the overall survival period, it was pointed out that tertiary treatment had been administered to 60% or more of all patients in each group and quaternary and subsequent treatment had also been administered in a considerable number of the patients. In the analysis of toxicity, the incidence of skin eruptions and thrombosis was higher in the E+B group, but it did not differ from the previously reported rate (68).

At the ASCO meeting in 2009, the results of a phase III clinical study (ATLAS) designed to compare bevacizumab monotherapy with bevacizumab doublet + erlotinib therapy, both administered as maintenance therapy after platinum + bevacizumab therapy in previously untreated cases of NSCLC (other than squamous cell carcinoma), were reported. In terms of the primary endpoint of PFS, the results in the combined therapy were superior to those in the monotherapy group (69). Some of the studies now under way include a phase III clinical study (ECOG 1505) designed to evaluate the effect of addition of bevacizumab to postoperative adjuvant therapy in completely resected cases of NSCLC and a phase III clinical study (SABRE-L) designed to evaluate the effect of the addition of sunitinib to CBDCA + PTX + bevacizumab therapy administered as initial chemotherapy.

3. VEGFR tyrosine kinase inhibitors

1) Vandetanib (ZD6474)

Vandetanib is a multi-targeted tyrosine kinase inhibitor capable of inhibiting both VEGFR and EGFR at the same time. In a randomized phase II clinical study comparing DOC monotherapy with DOC + vandetanib therapy (100 or 300 mg/day) in previously treated cases of NSCLC, significant prolongation of the PFS was observed in the combined treatment group given vandetanib (100 mg/day) (mPFS: 12 weeks in the DOC monotherapy group vs. 18.7 weeks in the DOC + vandetanib 100 mg/day group, p=0.037, one-tailed; vs. 17.0 weeks in the DOC + vandetanib 300 mg/day group, p=0.231, one-tailed) (70). On the basis of these results, a phase III clinical study (ZODIAC) comparing DOC + placebo therapy with DOC + vandetanib (100 mg/day) therapy was carried out, and a significant difference in the PFS (primary endpoint) between the two groups was reported during the ASCO meeting in 2009 (71). In a phase II study comparing vandetanib with gefitinib, the PFS (primary endpoint) was significantly longer in the vandetanib group (11.0 weeks vs. 8.1 weeks, p=0.025) (72). In an early phase II dose-determination study conducted in Japan, in which the drug was administered at three dose levels (100, 200 and 300 mg/day), the response rates in the three dosage groups were 17.6%, 5.6% and 16.7%, respectively (73). In a randomized phase II clinical study comparing CBDCA + PTX therapy (PC group) with CBDCA + PTX + vandetanib therapy (VPC group), with both administered as the initial chemotherapy, the response rate and mPFS were 25% and 23 weeks, in the PC group, and 32% and 24 weeks, respectively, in the VPC group (74).

During the meeting of ASCO in 2009, the results of a phase III clinical study (ZEAL) comparing vandetanib with

erlotinib administered as the second-line chemotherapy (75) and a phase III clinical study of PEM ± vandetanib were reported. Neither of these studies revealed superiority of vandetanib over the reference drug in terms of the PFS (primary endpoint) (76). A phase III clinical study (ZEPHYR) comparing this drug with placebo in patients with NSCLC treated previously with EGFR inhibitors also showed negative results.

2) Sorafenib

Sorafenib serves as a tyrosine kinase inhibitor for Raf-kinase, VEGFR-2, VEGFR-3, PDGFR-B, Flt-3 and c-kit (77). A phase II clinical study of sorafenib monotherapy in previously untreated cases of NSCLC was started, but it was discontinued when only 25 cases had been registered, because of the poor responses (78). In this study, the response rate, mPFS and MST were 12%, 2.9 months and 8.8 months, respectively. A phase II clinical study of sorafenib monotherapy was also performed in 52 cases of recurrent NSCLC, which yielded tumor reduction in 29% of all cases, and the mPFS and MST of 11.9 weeks and 29.3 weeks, respectively. As grade 3 or more severe toxicities, the hand-foot syndrome (10%) and hypertension (4%) were noted (79). A randomized phase II clinical study was carried out in 83 patients with NSCLC with a history of having received two or more regimens of chemotherapy before. These 83 patients were initially treated with sorafenib and later with either with placebo (placebo group) or sorafenib (continued sorafenib therapy group). The percentage of patients rated as showing SD or a better outcome at 2 months (primary endpoint) was 19% in the placebo group and 47% in the continued sorafenib therapy group, indicating the significantly better outcome in the continued sorafenib therapy group ($p=0.01$). Significant difference in the PFS was also found (mPFS: 2.0 months vs. 3.6 months, $p=0.009$), however, there was no significant difference in the overall survival between the two groups (MST: 9.0 months vs. 11.9 months, $p=0.18$) (80).

In addition, a phase III clinical study (ESCAPE) comparing PTX + CBDCA + placebo therapy with PTX + CBDCA + sorafenib therapy in 926 previously untreated cases of NSCLC was carried out, which yielded no significant inter-group difference in the response rate (23% vs. 25%), PFS (mPFS: 4.8 months vs. 4.8 months, $p=0.92$) or overall survival (MST: 10.6 months vs. 10.7 months, $p=0.93$) between the two treatment groups (81). At present, a phase III clinical study designed to evaluate the effect of addition of sorafenib to GEM + CDDP therapy is underway.

3) Sunitinib

Sunitinib is a multi-targeted tyrosine kinase inhibitor for VEGFR-1, -2 and -3, PDGFR-α and -β, KIT, RET, CSF-1R and Flt-3. A phase II clinical study of sunitinib 50 mg/day (oral treatment for 4 weeks, followed by drug cessation for 2 weeks) was carried out in 63 previously treated cases of NSCLC. In this study, 22% of all patients required dose reduction. The major toxicities observed were malaise, myalgia, nausea and hypertension. The response rate, median time to progression (mTTP) and MST were 11.1%, 12.0 weeks and 23.4 weeks, respectively (82). On the basis of these results, a phase II clinical study was conducted to evaluate the effect of daily treatment with sunitinib (37.5 mg/day) in 47 previously treated cases of NSCLC. In this study, dose reduction was needed in 29.8% of all the patients. The response rate, mPFS and MST were 2.1%, 12.3 weeks and 37.1 weeks, respectively. These results suggest that this drug may be a promising agent for the treatment of recurrent NSCLC. The major toxicities were malaise, dyspnea and hypertension. Grade 3/4 hemoptysis was noted in 2% of all the patients (83).

In addition, several clinical studies designed to evaluate the efficacy of sunitinib combined with other therapies (chemotherapy including platinum preparations, single chemotherapy or EGFR-TKI) have been carried out. A phase III clinical study comparing erlotinib monotherapy with erlotinib + sunitinib therapy in previously treated cases of NSCLC is now underway (84).

4) Cediranib (AZD2171)

Cediranib is a tyrosine kinase inhibitor for VEGFR. A randomized double-blind phase II/III study (BR.24) was carried out, comparing CBDCA + PTX + cediranib therapy with CBDCA + PTX + placebo therapy in patients with advanced NSCLC. In this study, 150 patients were allocated to the CBDCA + PTX + placebo group (CPP group) or the CBDCA + PTX + cediranib 30 mg/day group (CPC group). The response rate was significantly higher in the CPC group (38%) than in the CPP group (16%) ($p<0.001$), but the PFS did not differ significantly between the two groups (mPFS: 5.0 months vs. 5.6 months, $p=0.13$). In the analysis of toxicity, the incidence of diarrhea, dehydration, mucositis, hand-foot syndrome, hypertension and decreased blood neutrophil count was higher in the CPC group. A clinical study on cediranib administered at a lower dose level (20 mg) is now planned (85).

4. Other molecule-targeted drugs

1) Bexarotene

Retinoids play an important role in the growth, division and differentiation of cells and the activation of cell apoptosis. Bexarotene is considered to exert antitumor activity through its selective actions on the retinoid X receptor (86).

A phase I/II clinical study on bexarotene combined with VNR + CDDP as the initial chemotherapy for NSCLC was carried out. In this study, the maximum-tolerated dose (MTD) was 400 mg/m^2/day. In the phase II trial, the response rate and MST were 25% and 14 months, respectively (87). In a phase II clinical study of bexarotene + GEM + CBDCA in 47 previously untreated cases of NSCLC, the response rate, MST and one-year survival rate were 25%, 12.7 months and 53%, respectively. In the analy-

sis of toxicity in the same study, all of the adverse reactions other than hypertriglyceridemia were tolerable (88). On the basis of these results, two randomized phase III studies were carried out in previously untreated cases of NSCLC to evaluate the effect of the addition of bexarotene to platinum-based chemotherapy. In one of these studies (SPIRIT I), 623 patients were allocated to either the VNR + CDDP group (VP group) or the VNR + CDDP + bexarotene group (VPB group). The response rate was significantly higher in the VP group (24.4% vs. 16.7%, p=0.0224), and the VP group also tended to have a better outcome in terms of the PFS (mPFS: 5.0 months vs. 4.3 months, p=0.095) and overall survival (MST: 9.9 months vs. 8.7 months, p=0.3). In the analysis of toxicity, the incidences of hypertriglyceridemia and hypothyroidism were higher in the group treated with bexarotene (89). In a second study (SPIRIT II), 612 patients were allocated to either the CBDCA + PTX group (CP group) or the CBDCA + PTX + bexarotene group (CPB group). The outcomes tended to be better in the CP group, in terms of the response rate (23.5% vs. 19.3%, p=0.24), PFS (mPFS: 4.9 months vs. 4.1 months, p=0.061) and the overall survival (MST: 9.2 months vs. 8.5 months, p=0.2) (90). Neither of the two studies demonstrated that the use of bexarotene in combination with platinum-based chemotherapy augmented the effects of platinum-based chemotherapy.

2) Figitumumab (CP-751,871)

Figitumumab is a completely humanized IgG2 type monoclonal antibody directed against insulin-like growth factor I (IGF-I) receptor. A randomized phase II clinical study was carried out comparing CBDCA + PTX therapy (TC group) with figitumumab + CBDCA + PTX therapy (TCI group) in 150 previously untreated cases of advanced NSCLC. The response rate was 41% in the TC group and 54% in the TCI group. The response rate was higher among patients with squamous cell carcinoma (46% vs. 78%), suggesting that the addition of anti-IGF-IR antibody is likely effective in patients with squamous cell carcinoma (91). In the analysis of toxicity, the incidences of hyperglycemia and dehydration were higher in the TCI group. Figitumumab may thus be a promising agent for the treatment of squamous cell carcinoma of the lung.

A randomized phase III clinical study comparing TC with TCI in previously untreated cases of NSCLC and a randomized phase III clinical study comparing figitumumab therapy with erlotinib + figitumumab therapy for recurrent NSCLC are now underway. There are also ongoing clinical studies on several other products of anti-IGF-IR antibody, such as R 1507, and the results of these studies are awaited.

3) ASA404

ASA404 is an agent causing vascular destruction and has been reported to induce irreversible tumor vessel destruction, hemorrhagic necrosis at the center of the tumor, and the production of cytokines. This drug is considered to induce tumor necrosis through its actions on existing blood vessels rather than on the newly formed blood vessels (92-95). Its target molecules remain unidentified. A randomized phase II clinical study was carried out in 76 previously untreated cases of advanced NSCLC, comparing ASA404 + CBDCA + PTX therapy (ASA404-CP group) with CBDCA +PTX therapy (CP group). The outcomes were better in the ASA404-CP group in terms of the response rate (31% vs. 22%), mTTP (5.4 months vs. 4.4 months) and MST (14.0 vs. 8.8 months). In the analysis of toxicity, no differences were noted between the two groups (95). On the basis of these results, a randomized phase III clinical study is now underway.

Conclusion

In recent years, the development of molecular-targeted drugs has progressed remarkably, and numerous clinical studies have been carried out on molecular-targeted drugs for the treatment of NSCLC. In this paper, the results obtained to date have been presented, focusing on drugs for which phase III clinical studies have been carried out. In parallel with clinical studies, studies exploring biomarkers have also been carried out. It is essential to develop biomarkers to serve as predictors of the responses to treatment with molecular-targeted drugs, like EGFR gene mutations serving as a predictor of the response to EGFR tyrosine kinase inhibitors. The outcomes of NSCLC treatment will improve if the appropriate therapeutic strategies are applied to appropriately selected patients on the basis of clinical factors (histological type, etc.) and biomarkers found in the tumor tissues and serum.

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