Editorial Commentary

Which is better, EGFR-TKI mono or combination for non-small cell lung cancer with mutated EGFR?

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Currently, three strategies for primary treatment of advanced non-small cell lung cancer (NSCLC) with EGFR gene mutations are being investigated: epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) monotherapy, EGFR-TKI + vascular endothelial growth factor (VEGF) inhibitor combination, and EGFR-TKI + cytotoxic anticancer agent combination (*Tables 1*,*2*).

At the ASCO 2018 meeting, the results from a phase 3 study comparing erlotinib monotherapy for standard primary treatment versus erlotinib + bevacizumab combination were reported (NEJ026) (1). NEJ026 was based on a similarly designed phase 2 study (JO25567), which previously showed that erlotinib + bevacizumab combination significantly increased the primary endpoint, progression-free survival (PFS), compared with erlotinib monotherapy [16.4 *vs.* 9.8 months; hazard ratio (HR), 0.52; 95% CI, 0.35–0.76] (2). Both were Japanese multicenter studies.

NEJ026 was an open-label randomized phase 3 study comparing erlotinib + bevacizumab combination with erlotinib monotherapy in 224 advanced-non-squamous NSCLC patients with EGFR gene mutations (Ex19 del/ Ex21 L858R) in performance status 0–2, with an interim analysis performed with PFS as the primary endpoint when 117 events had occurred. Since PFS (independent central judgment) was significantly higher in the combination group (16.9 *vs.* 13.3 months; HR, 0.61; 95% CI, 0.42–0.88), the study was ended prematurely. By type of EGFR gene mutation, PFS was 16.6 *vs.* 12.4 months for Ex19 del (HR, 0.69; 95% CI, 0.41–1.16) and 17.4 *vs.* 13.7 months for Ex21 L858R (HR, 0.57; 95% CI, 0.33–0.97): for both types of mutation, PFS was better in the combination group. Reported adverse events (AEs) included hypertension (45.5% *vs.* 8.8%), proteinuria (32.1% *vs.* 2.6%), and hemorrhage (25.0% *vs.* 2.6%), which were all noted at higher incidences in the combination group than in the monotherapy group; however, the treatment discontinuation rate due to AEs was similar between the two groups (18.8% *vs.* 15.2%). Overall survival (OS) data remain immature, with no final analysis results reported to date. Another subgroup analysis showed the PFS to be 16.9 *vs.* 12.6 months in the group with malignant pleural effusions (HR, 0.58; 95% CI, 0.34–1.02) and 16.6 *vs.* 14.2 months in the group without (HR, 0.67; 95% CI, 0.41–1.10): even in the population with pleural effusion, PFS increased in the combination group. In the group without cerebral metastases, PFS was higher in the combination group (18.0 vs .15.1 months; HR, 0.56; 95% CI, 0.35–0.90). However, in the group with cerebral metastases, PFS did not differ between the two groups (12.7 *vs.* 11.2 months; HR, 0.78; 95% CI, 0.42–1.43). As stated above, erlotinib + bevacizumab combination is advantageous not only with increased PFS for any type of EGFR gene mutation, but also with expected increases in PFS even in patients with pleural effusion; however, some issues remain to be resolved, including unknown OS-increasing effect, necessity for further investigations of effects on cerebral metastases, and definitely increased incidences of AEs.

Potentials of combinations of EGFR-TKI and VEGF inhibitors are discussed below in view of preclinical study results.

The first to discuss is a crosstalk between EGFR and VEGF, both key factors in tumor growth and metastases. When binding to EGFR, EGF and TGF-α activate EGFR to increase VEGF expressions. The crosstalk has

Table 1 Clinical studies of EGFR-TKI in primary treatment

Study	Investigational drugs	Phase	CNS mets	Primary endpoint	N	PFS (m)	HR	OS (m)	HR	Ex19 PFS (m)	HR	Ex21 PFS (m)	HR	ORR (%)
EGFR-TKI monotherapy														
NEJ002	Gefitinib	III	Included	PFS	114	10.8	0.30	28	0.89					74
	CBDCA + PTX				114	5.4		27						31
WJOG3405	Gefitinib	III	Included	PFS	86	9.6	0.56	35	1.25					62
	CDDP + DOC				86	6.6		37						32
OPTIMAL	Erlotinib	III	Included	PFS	82	13.7	0.16	23	1.19					83
	CBDCA + GEM				72	4.6		27						36
EURTAC	Erlotinib	III	Included	PFS	86	9.7	0.37	23	0.92					61
	CDDP/CBDCA + GEM/DOC				87	5.2		20						18
LUXLUG3	Afatinib	III	Included	PFS	230	11.1	0.58	28	0.88					56
	CDDP + PEM				115	6.9		28						23
LUXLUG6	Afatinib	III	Included	PFS	242	11	0.28	23	0.93					74
	CDDP + GEM				122	5.6		24						31
LUXLUG7	Afatinib	IIb	Included	PFS, TTF, OS	160	11	0.73	28	0.87	12.7	0.76	10.9	0.7	70
	Gefitinib				159	10.9		25		11		10.8		56
FLAURA	Osimertinib	III	Included	PFS	279	18.9	0.46	NR	0.63	21.4	0.43	14.4	0.5	80
	Gefitinib/erlotinib				277	10.2		NR		11		9.5		76
ARCHER1050	Dacomitinib	III	Excluded	PFS	227	14.7	0.59	34	0.76	16.5	0.55	12.3	0.6	75
	Gefitinib				225	9.2		27		9.2		9.8		72
EGFR-TKI + VEGF inhibitor														
JO25567	Erlotinib + bevacizumab	II	Excluded	PFS	75	16.4	0.52	47.0	0.81	18.0	0.41	13.9	0.67	69
	Erlotinib				77	9.8		47		10.3		7.1		64
NEJ026	Erlotinib + bevacizumab	III	Included	PFS	112	16.9	0.61	NA		16.6	0.69	17.4	0.6	72
	Erlotinib				112	13.3		NA		12.4		13.7		66
RELAY	Erlotinib + ramucirumab	III	Excluded	PFS	224	19.4	0.59	NR	0.83	19.6	0.65	19.4	0.6	76
	Erlotinib				225	2.4		NR		12.5		11.2		75
EGFR-TKI + chemotherapy														
NEJ009	CBDCA + PEM + gefitinib	III	Included	PFS, PFS2, OS	170	20.9	0.49	52	0.69					84
	Gefitinib				172	11.2		39						67
Noronha *et al.*	CBDCA + PEM + gefitinib	III	Included	PFS	174	16	0.51	NR	0.45					75
	Gefitinib				176	8		17						63

CBDCA, carboplatin; CDDP, cisplatin; CNS mets, central nervous system metastases; Ex, type of EGFR gene mutation: Ex19 del or Ex21 L858R; EGFR, epidermal growth factor receptor; HR, hazard ratio; DOC, docetaxel; GEM, gemcitabine; NA, not assessed; NR, not reached; ORR, overall response rate; OS, overall survival; PEM, pemetrexed; PFS, progression-free survival; PTX, paclitaxel; TTF, time to treatment failure; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Table 2 Ongoing clinical studies of EGFR-TKI combinations in primary treatment

Study	Investigational drugs	Phase	CNS mets	Primary endpoint	N
EGFR-TKI + VEGF inhibitor					
BEVERLY	Erlotinib + bevacizumab	III	Excluded	PFS	100
	Erlotinib				100
CTONG1509	Erlotinib + bevacizumab	III	Included	PFS	155
	Erlotinib				155
TORG1833	Osimertinib + ramucirumab	II	Included	PFS	60
	Osimertinib				60
NCT03909334	Osimertinib + ramucirumab	II	Included	PFS	100
	Osimertinib				50
NCT02971501	Osimertinib + bevacizumab	II	Included	PFS	56
	Osimertinib				56
WJOG9717L	Osimertinib + bevacizumab	II	Included	PFS	60
	Osimertinib				60
EGFR-TKI + chemotherapy					
NEJ032C/LOGIK1801	CDDP/CBDCA + PEM + osimertinib	II	Included	Safety/ORR	66
FLAURA2	Osimertinib + platinum doublet chemotherapy	III	Details still Unknown	PFS	556
	Osimertinib				

CBDCA, carboplatin; CDDP, cisplatin; CNS mets, central nervous system metastases; EGFR, epidermal growth factor receptor; ORR, overall response rate; PEM, pemetrexed; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

been reported to occur between EGFR and VEGF in some forms, including non-EGFR-dependent increases in VEGF expression in resistance to EGFR inhibition. Experiments with a mouse xenograft model of human lung adenocarcinoma showed that increased expressions of the EGFR pathway due to gene expressional changes in interstitial cells, not in tumor cells, may be involved in the tumor resistance to VEGF inhibitors (3). It is reasonable to attempt to suppress tumor growth by blocking this EGFR-VEGF crosstalk with EGFR-TKI and VEGF inhibitors. In clinical settings, effects on malignant pleural effusion are expected. VEGF produced by tumor cells that have infiltrated the thoracic cavity is considered to act on the chest and diaphragm vascular endothelial cells to increase vascular permeability, resulting in the leakage of albumin and other plasma components from blood vessels, hence malignant pleural effusions (4). In fact, VEGF concentrations in malignant pleural effusions have been reported to be higher than exudative and leaking pleural effusions, which are caused by other factors (5), and some studies reported malignant pleural effusions to be controllable by bevacizumab combination chemotherapy in clinical settings. In study NEJ026 as well, a subgroup analysis by existence of pleural effusion showed that antitumor effects in patients with pleural effusion were expectable.

Second, we address effects on MET gene amplifications with resistance to EGFR-TKI. For the mechanism of acquisition of resistance to 1st/2nd-generation EGFR-TKI, approximately 40–50% of patients have secondary mutations of T790M, and tumors acquire resistance to EGFR-TKI via many other mechanisms, including MET gene amplifications (up to 5%) and transformation to small-cell carcinoma (4–10%) (6). With regard to the mechanism of resistance acquisition in the patients in the osimertinib group, who experienced disease exacerbation during the FLAURA study, MET amplifications (15%), EGFR C797S mutations (7%), and other changes, along with T790M deletions, were noted (7). Preclinically, Furugaki et al. reported that a combination of erlotinib and bevacizumab was more effective than erlotinib or bevacizumab monotherapy in terms of tumor suppression

in a cell line having both EGFR gene mutations and MET gene amplifications (8). Therefore, erlotinib + bevacizumab combination may be a treatment option for patients with MET amplification (9).

Third, potential effects on cerebral metastases should be taken into account. Generally, cerebral metastases in melanoma are of the perivascular progression type, whereas those in NSCLC are of the neovascularization-dependent type (10) and reportedly often increase vascular permeability and intensify cerebral edema (11). Therefore, bevacizumab combination is expected to be effective in treating or suppressing cerebral metastases. In fact, one study comparing CDDP+GEM therapy and CDDP + GEM + bevacizumab therapy for advanced lung adenocarcinoma reported that the incidence of cerebral metastases was lower in the bevacizumab combination group (AVAiL) (12). Another study found MET amplifications and/or MET protein expressions in 20–40% of the NSCLC patients with cerebral metastases (13); erlotinib+bevacizumab combination is expected to be effective in treating and suppressing cerebral metastases. In study NEJ026, however, no results were obtained to find any significance of bevacizumab combination in patients with cerebral metastases. One reason may be that tumor diameters are smaller in cerebral metastases in lung carcinoma with EGFR gene mutations (14). Hence, the patients with cerebral metastases enrolled in NEJ026 may have not enjoyed the best effects of VEGF inhibitors, because they had small tumor diameters in cerebral metastases and hence no severe cerebral edema. The NEJ026 results do not allow us to identify antitumor effects such as intracranial responses and PFS. A prospective confirmatory study comparing osimertinib monotherapy and osimertinib + bevacizumab combination in patients with cerebral metastases (NCT02971501) is ongoing and is expected to provide valuable data on their effects on central nervous system (CNS) lesions.

As stated above, combination with EGFR-TKI + VEGF inhibitors has much potential. Reported at the ASCO 2019 meeting was a phase 3 comparative study of erlotinib + ramucirumab combination compared with erlotinib monotherapy (RELAY). Erlotinib + ramucirumab combination significantly increased the primary endpoint, PFS, compared with standard erlotinib monotherapy (19.4 *vs.* 12.4 months; HR, 0.59; 95% CI, 0.46–0.76) (15). As in study NEJ026, however, no OS results were reported. In the erlotinib + ramucirumab combination group, Grade ≥3 hypertension was noted in 24% of the patients, and proteinuria, in 3%; however, the proportion of patients who discontinued treatment because of AEs was nearly the same between the two groups. Although attention should be paid to increased incidences of hypertension and proteinuria with concomitant VEGF inhibitors, the two phase 3 studies (NEJ026, RELAY) suggest the toxicity of erlotinib + VEGF inhibitor combination to be tolerable.

Therefore, combination with EGFR-TKI and VEGF inhibitors represents a therapeutic strategy with great expectations for the future. Unless its superiority is finally demonstrated by OS results from the phase 3 study, however, it seems too early now to choose the regimen associated with increased incidences of AEs as the standard treatment. Currently, in addition to NEJ026, phase 3 studies of erlotinib + bevacizumab combination (BEVERLY, CTONG1509) are ongoing, attracting attention as to the reproducibility of their results. Although no significant difference was found in the OS for JO25567 reported at the ASCO 2018 meeting (47.0 *vs.* 47.4 months; HR, 0.81; 95% CI, 0.53–1.23) (2), we await the publication of combined analysis results for OS from studies JO25567 and NEJ026.

On the other hand, a regimen is being developed with the EGFR-TKI drug to be combined with VEGF inhibitors for primary treatment switched from erlotinib to osimertinib. This is justified by the results from a phase 3 study comparing the 3rd-generation drug osimertinib with the 1st-generation drug gefitinib/erlotinib (FLAURA) (16). The primary endpoint, PFS, increased significantly (18.9 *vs.* 10.2 months; HR, 0.46; 95% CI, 0.37–0.57), and OS was better in the osimertinib group (HR, 0.63; 95% CI, 0.45–0.88), although the data were immature. The proportion of patients with Grade $\geqslant$ 3 AEs was lower in the osimertinib group than in the gefitinib/erlotinib group, demonstrating better tolerability. Presented at the 2019 ASCO meeting were the results from a single-arm phase 1/2 study of osimertinib + bevacizumab combination (n=49), which reported overall response rate (ORR) of 80%, PFS of 18.4 months, 1-year PFS rate of 70%, and 1-year OS rate of 91% (17). Randomized phase 2 studies comparing osimertinib monotherapy and osimertinib + bevacizumab combination (WJOG9171L, NCT02971501) and those comparing osimertinib monotherapy and osimertinib + ramucirumab combination (TORG1833, NCT03909334) are ongoing. Of the EGFR-TKI studies, osimertinib was found to be highly effective and tolerable, with a high CNS transfer rate: osimertinib + VEGF inhibitor combination is considered one of the most promising combination therapies.

In addition to the above EGFR-TKI + VEGF inhibitor combination, conventional EGFR-TKI monotherapy and EGFR-TKI + cytotoxic anticancer agent combination may also serve therapeutic strategies.

First, we'll discuss EGFR-TKI monotherapy. In a phase 3 study (ARCHER1050), dacomitinib, a 2nd-generation

EGFR-TKI, increased not only PFS (14.7 *vs.* 9.2 months; HR, 0.59; 95% CI, 0.47–0.74), but also OS (34.1 *vs.* 26.8 months; HR, 0.76; 95% CI, 0.58–0.99), compared with gefitinib. However, the PFS in the dacomitinib group in ARCHER1050 was shorter than that in the osimertinib group in FLAURA. The incidence of Grade $\geqslant$ 3 AEs was high at 48.9%, posing toxicity management issues, including dose reductions and cessations (18). Therefore, osimertinib is currently used most commonly in primary treatment for lung carcinoma with *EGFR* gene mutations, since it surpasses 1st-generation EGFR-TKI in terms of both PFS and tolerability, and is also likely to surpass the 2nd-generation drug dacomitinib in the same two aspects. There is room for argument, however, with regard to the PFS results by type of EGFR gene mutation in FLAURA. In the osimertinib group, the PFS was 21.4 months for Ex19 del and 14.4 months for Ex21 L858R. Better results were obtained from NEJ026, in which the PFS for Ex21 L858R with erlotinib + bevacizumab combination was 17.4 months, and from RELAY, in which the PFS for Ex21 L858R with erlotinib + ramucirumab combination was 19.4 months. Ex19 del and Ex21 L858R have so far been reported to also differ biologically (19). It seems it will become necessary in the future to use osimertinib monotherapy and EGFR-TKI + VEGF inhibitor combination in distinct ways according to the type of EGFR gene mutation.

Next to discuss is EGFR-TKI + chemotherapy combination. Reported at the ASCO 2018 meeting were the results of a phase 3 study comparing CBDCA + PEM + gefitinib combination with gefitinib monotherapy (NEJ009) (20). With PFS, PFS2, and OS as the primary endpoints, data were sequentially analyzed using a gate-keeping method. PFS differed significantly between the combination and monotherapy groups (20.9 *vs.* 11.2 months; HR, 0.49; 95% CI, 0.39–0.63), whereas PFS2 did not differ significantly between the combination and monotherapy groups (20.9 *vs.* 20.7 months; HR, 0.97; 95% CI, 0.77–1.22). This led to the publication of OS as a reference value despite the surprisingly longer survival in the combination group (52.2 *vs.* 38.8 months; HR, 0.70; 95% CI, 0.52–0.93). At the ASCO 2019 meeting, a single study center in India published the results from a similar phase 3 study comparing gefitinib and CBDCA + PEM + gefitinib combination, which found significant differences in PFS between the combination and monotherapy groups (16 *vs.* 8 months; HR, 0.51; 95% CI, 0.39–0.66) and in OS between the combination and monotherapy groups (OS not reached *vs.* 17 months; HR, 0.45; 95% CI, 0.31–0.65) (21). However, this result is difficult to accept universally, since the median OS for the monotherapy group was too short. Therefore, EGFR-TKI + cytotoxic anticancer agent combination remains to pose a challenging issue concerning OS, although it is considered an effective therapeutic strategy. In Japan, a single-arm phase 2 study of platinum + PEM + osimertinib for primary treatment in advanced-NSCLC patients with EGFR gene mutations (NEJ032C/LOGIK1801) is ongoing. Likewise, a global phase 3 study comparing platinum combination chemotherapy + osimertinib with osimertinib monotherapy for primary treatment (FLAURA2) is going to begin, with high expectation for favorable results (22).

Finally, the clinical implications of therapeutic strategies with EGFR-TKI monotherapy, EGFR-TKI+VEGF inhibitor combination, and EGFR-TKI + cytotoxic anticancer agent combination are discussed from the viewpoint of EGFR TKI-TKI sequence therapy. First, when osimertinib monotherapy is chosen as the primary treatment, no evidence is available for the strategy with other EGFR-TKI drugs administered after resistance development, making conventional cytotoxic anticancer agents the mainstay of secondary treatment. Although PFS2 was not reached in the osimertinib group in FLAURA, the lower limit of 95% CI was reported to be 23.7 months (23). When resistance developed with T790M mutations after treatment with 1st/2nd-generation EGFR-TKI, osimertinib increased PFS compared with cytotoxic anticancer agents (10.1 *vs.* 4.4 months; HR, 0.30; 95% CI, 0.23–0.41) (AURA3) (24). Therefore, with erlotinib + bevacizumab and CBDCA + PEM + gefitinib combinations for primary treatment, PFS was 16.9 and 20.9 months, respectively, and PFS2 is expected to be approximately 27 and 31 months. However, the osimertinib use rate in the gefitinib/erlotinib group in FLAURA was approximately 26% (23). In a Japanese prospective observational study (REMEDY), the osimertinib use rate following resistance to 1st/2nd-generation EGFR-TKI was low at approximately 25% of the 236 patients in the full-analysis set (25). The strategy of administering osimertinib following treatment with 1st/2nd-generation EGFR-TKI still poses some problems to be solved, including difficulty with re-biopsy and T790M gene mutation detection rates.

In this editorial commentary, three patterns of promising treatment strategy for lung carcinoma with EGFR gene mutations were discussed: EGFR-TKI monotherapy, EGFR-TKI+VEGF inhibitor combination, and EGFR-TKI + cytotoxic anticancer agent combination. Among them, EGFR-TKI+VEGF inhibitor combination is expected as a therapeutic strategy with potential clinical applications expected from the above preclinical study results. In reality, however, the advantages/disadvantages of the three strategies are difficult to compare on the basis

of available clinical study results. This is because different types of EGFR-TKI are chosen for the three strategies: osimertinib often for monotherapy, erlotinib for VEGF inhibitor combination, and gefitinib for cytotoxic anticancer agent combination. Desirably, we will be able to establish the best strategy, based on comparisons of the efficacy and tolerability of osimertinib monotherapy vs osimertinib + VEGF inhibitor combination *vs.* osimertinib + platinum combination chemotherapy.

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