Editorial

First-line EGFR TKI therapy in Non-Small Cell Lung Cancer: Looking back before leaping forward

The sheer impact of EGFR kinase inhibitors in non-small cell lung cancer (NSCLC) cannot be understated. Beyond serving as effective and well-tolerated agents for a subset of patients with NSCLC, the implementation of EGFR tyrosine kinase inhibitors (TKIs) brought the field of precision oncology and targeted therapy to mainstream oncology. Building on promising clinical results and growing insight into molecular biology and predictive biomarkers, EGFR TKIs achieved the previously unthinkable: they replaced first-line chemotherapy for some patients with advanced NSCLC. Multiple phase III trials that compared EGFR TKIs with chemotherapy consistently showed superior outcomes when using targeted therapy in EGFR-mutant NSCLC, with higher response rates, longer progression-free survival (PFS) and more favorable toxicity profiles [1-7] (**Table 1**). However, with longer follow-up, none of these studies reported improvements in overall survival (OS), largely attributed to cross-over [8-10].

In the study accompanying this editorial, Hiroshige and colleagues report the long-awaited (and overdue) final results of WJTOG 3405, a randomized phase III trial comparing the first-generation EGFR TKI gefitinib to chemotherapy (cisplatin plus docetaxel) in patients with advanced EGFR-mutant NSCLC [11]. Initial results demonstrated a clear improvement in outcomes, including PFS [2]. In this updated analysis, with a follow-up of 5 years, median survival was reported as 34.9 months with gefitinib and 37.3 months with chemotherapy, with no statistically significant difference between the two arms (and both somewhat higher than similar studies). The crossover rate from chemotherapy to EGFR TKI was 91% while the crossover rate from gefitinib to chemotherapy was only 73%. This finding is not unique to WJTOG 3405; crossover from TKI to chemotherapy has been consistently lower than chemotherapy to TKI in phase III trials (**Table 1**), possibly reflecting the lack of appealing salvage therapies during that era.

The high crossover rates in WJTOG 3405 resulted in the vast majority of patients receiving EGFR TKI therapy in any line of therapy. Unfortunately, data suggest this does not always occur in clinical practice. In a recent retrospective analysis of real-world

evidence, 630 patients with advanced EGFR-mutant NSCLC were identified [12]. Of those, 35.7% never received an EGFR TKI. This directly impacted outcomes. Patients who did receive EGFR TKI therapy had a median survival of 21.0 months compared to 13.3 months for those who did not. Noting the particularly high survival in both arms, an important lesson is the importance of receiving the appropriate targeted therapy. In practice, the only reliable means to ensure its use is incorporation in the front-line setting.

It is critical to note that despite similar survival times between the two arms, these results do not support abandoning EGFR TKI use in the front-line setting. While extending survival is certainly a goal of therapy, there are several other factors that support first-line targeted therapy. The response rate is consistently higher with EGFR TKI therapy, an important feature for symptomatic patients, and responses can often be rapid and profound. The CNS efficacy of EGFR TKIs, particularly later generation agents, offers another clinically meaningful efficacy advantage. Toxicity consistently favors EGFR TKI therapy (**Table 1**). And while formal measures of patient-reported outcomes (PROs) are unavailable from WJTOG 3405, previous studies revealed that EGFR TKI therapy was associated with improved quality of life (QOL) when compared with platinum-doublet chemotherapy [13-16] (**Table 2**). In the years since WJTOG 3405 was completed, several newer EGFR TKIs have emerged. The phase III FLAURA trial compared the first third-generation EGFR TKI, osimertinib, to first-generation agents gefitinib or erlotinib. Osimertinib delivered a much greater PFS (18.9 months vs. 10.2 months, 95% CI: 0.37-0.57) [17],greater intracranial activity [18] and better tolerability. Recently, a significant improvement in overall survival was reported with the use of first-line osimertinib [19], supporting the position of osimertinib as the preferred first-line EGFR TKI, with chemotherapy relegated to a salvage setting.

This trial shows that both EGFR TKI therapy and chemotherapy are active agents in patients with EGFR-mutant NSCLC. An emerging strategy is combining these approaches. NEJ009 was a randomized phase III trial of gefitinib, with or without carboplatin and pemetrexed, in 345 untreated patients with advanced NSCLC with

EGFR mutations. Patients who received the combination of EGFR TKI and chemotherapy had a significantly longer PFS (20.9 months vs. 11.2 months, HR=0.494, 95% CI: 0.391-0.625) and, more importantly, had a significant improvement in survival (52.5 months vs. 38.8 months, HR 0.695, 95% CI: 0.520-0.927) [20]. Similarly, another randomized phase III trial of gefitinib, with or without carboplatin and pemetrexed, in 350 patients with EGFR-mutant NSCLC showed that the combination of EGFR TKI and chemotherapy prolongs PFS (16 months vs. 8 months, HR=0.51, 95% CI: 0.39-0.66) and significantly improves overall survival (not reached vs. 17 months, HR=0.45, 95% CI: 0.31-0.65) [21]. Concurrent use of EGFR TKI and platinum-doublet chemotherapy ensures that patients receive both active regimens.

A logical extension of combination approaches is to explore the combination of third-generation osimertinib and chemotherapy. Compared to earlier first- or second-generation EGFR TKIs, osimertinib has a more favorable side effect profile, making it a good candidate for combination therapies. In a retrospective analysis of patients who received concurrent osimertinib and chemotherapy (following progression on TKI therapy), osimertinib was tolerable in combination with many standard chemotherapy regimens [22]. A phase III trial of osimertinib, with or without chemotherapy, as first-line treatment in patients with EGFR-mutant NSCLC (NCT04035486) has been launched.

WJTOG 3405 demonstrated that both EGFR TKIs and chemotherapy are integral parts of treatment in EGFR-mutant NSCLC. EGFR TKI therapy has several advantages over chemotherapy and will appropriately remain part of our preferred initial therapy. While no survival advantage was observed in this study, newer strategies incorporating EGFR TKIs have indeed pushed the survival boundaries, from the use of newer EGFR TKIs to combinations of TKIs and chemotherapy. WJTOG 3405 was an important stepping stone and these long-term results provide a healthy reassurance as we move towards even greater gains in the years to come.

Funding: None declared.

Disclosure: CK reports research support (to institution) from AstraZeneca. SVL reports consulting and/or advising fees from Apollomics, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, G1 Therapeutics, Genentech/Roche, Heron, Ignyta, Inivata, Janssen, Lilly, Merck, PharmaMar, Pfizer, Regeneron, Taiho, Takeda/Ariad, and Tempus; and research support (to institution) from Alkermes, AstraZeneca, Bayer, Blueprint, Bristol-Myers Squibb, Clovis, Corvus, Debiopharm, Genentech/Roche, Ignyta, Lilly, Lycera, Merck, Molecular Partners, OncoMed, Pfizer, Rain Therapeutics, and Spectrum Therapeutics.

C. Kim[1], S.V. Liu[1]*

[1] Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA.

(*E-mail: Stephen.V.Liu@gunet.georgetown.edu)

References

1. Maemondo M, Inoue A, Kobayashi K et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362: 2380-2388.
2. Mitsudomi T, Morita S, Yatabe Y et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010; 11: 121-128.
3. Rosell R, Carcereny E, Gervais R et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13: 239-246.
4. Sequist LV, Yang JC, Yamamoto N et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31: 3327-3334.
5. Wu YL, Zhou C, Hu CP et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014; 15: 213-222.
6. Wu YL, Zhou C, Liam CK et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol 2015; 26: 1883-1889.
7. Zhou C, Wu YL, Chen G et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011; 12: 735-742.
8. Inoue A, Kobayashi K, Maemondo M et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol 2013; 24: 54-59.
9. Yang JC, Wu YL, Schuler M et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015; 16: 141-151.
10. Zhou C, Wu YL, Chen G et al. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol 2015; 26: 1877-1883.
11. Yoshioka H, Shimokawa M, Seto T et al. Final overall survival results of WJTOG3405, a randomized phase III trial comparing gefitinib versus cisplatin with docetaxel as the first-line treatment for patients with stage IIIB/IV or postoperative recurrent EGFR mutation-positive non-small cell lung cancer. Ann Oncol 2019; 30: doi.org/10.1093/annonc/mdz399
12. Singal G, Miller PG, Agarwala V et al. Association of Patient Characteristics and Tumor Genomics With Clinical Outcomes Among Patients With Non-Small Cell Lung Cancer Using a Clinicogenomic Database. JAMA 2019; 321: 1391-1399.

13. Chen G, Feng J, Zhou C et al. Quality of life (QoL) analyses from OPTIMAL (CTONG-0802), a phase III, randomised, open-label study of first-line erlotinib versus chemotherapy in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC). Ann Oncol 2013; 24: 1615-1622.
14. Geater SL, Xu CR, Zhou C et al. Symptom and Quality of Life Improvement in LUX-Lung 6: An Open-Label Phase III Study of Afatinib Versus Cisplatin/Gemcitabine in Asian Patients With EGFR Mutation-Positive Advanced Non-small-cell Lung Cancer. J Thorac Oncol 2015; 10: 883-889.
15. Oizumi S, Kobayashi K, Inoue A et al. Quality of life with gefitinib in patients with EGFR-mutated non-small cell lung cancer: quality of life analysis of North East Japan Study Group 002 Trial. Oncologist 2012; 17: 863-870.
16. Yang JC, Hirsh V, Schuler M et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31: 3342-3350.
17. Soria J-C, Ohe Y, Vansteenkiste J et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. New England journal of medicine 2018; 378: 113-125.
18. Reungwetwattana T, Nakagawa K, Cho BC et al. CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2018; JCO2018783118.
19. AstraZeneca. Tagrisso significantly improves overall survival in the Phase III FLAURA trial for 1st-line EGFR-mutated non-small cell lung cancer. In. 2019.
20. Nakamura A, Inoue A, Morita S et al. Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009). In. American Society of Clinical Oncology 2018.
21. Noronha V, Patil VM, Joshi A et al. Gefitinib Versus Gefitinib Plus Pemetrexed and Carboplatin Chemotherapy in EGFR-Mutated Lung Cancer. J Clin Oncol 2019; JCO1901154.
22. Neal JW, Hausrath D, Wakelee HA et al. Osimertinib with chemotherapy for EGFR-mutant NSCLC at progression: Safety profile and survival analysis. In. American Society of Clinical Oncology 2019.

Table 1. Select first-line randomized trials of EGFR TKI vs. chemotherapy in EGFR-mutant NSCLC

Study	Treatment (n)	ORR	mPFS (months)	PFS HR (95% CI)	mOS (months)	OS HR (95% CI)	Rate of grade 3+ AEs	Rate of crossover
ENSURE [6]	Erlotinib (110)	63%	11.0	0.34 (0.22-0.51)	26.3	0.91 (0.63-1.31)	40%	66%
	Cisplatin/gemcitabine (107)	34%	5.5		25.5		57%	86%
CTONG-0802 [7, 10]	Erlotinib (82)	83%	13.1	0.16 (0.10-0.26)	22.8	1.19 (0.83-1.71)	17%	67%
	Carboplatin/gemcitabine (72)	36%	4.6		27.2		65%	78%
EURTAC [3]	Erlotinib (86)	58%	9.4	0.42 (0.27-0.64)	19.3	1.04 (0.65-1.68)	45%	NA
	Platinum doublet (87)	15%	5.2		19.5		67%	75.9%
LUX-Lung 3 [4, 9]	Afatinib (230)	56%	11.1	0.58 (0.43-0.78)	28.2	0.88 (0.66-1.17)	49%	78%
	Cisplatin/pemetrexed (115)	23%	6.9		28.2		48%	85%
LUX-Lung 6 [5, 9]	Afatinib (242)	67%	11.0	0.28 (0.20-0.39)	23.1	0.93 (0.72-1.22)	36%	63%
	cisplatin/gemcitabine (122)	23%	5.6		23.5		60%	65%
NEJ-002 [1, 8]	Gefitinib (114)	73.7%	10.8	0.32 (0.24-0.44)	27.7	0.887 (0.63-1.24)	41%	72%
	carboplatin/paclitaxel (114)	30.7%	5.4		26.6		71%	99%
WJTOG 3405 [2]	Gefitinib (86)	62%	9.2	0.49 (0.34-0.71)	34.9	1.25 (0.88-1.78)	NA	76%
	cisplatin/docetaxel (86)	32%	6.3		37.3		NA	91%

Abbreviations: ORR, overall response rate; mPFS, median progression free survival; HR, hazard ratio; mOS, median overall survival; AEs, adverse events; NA, not available.

Table 2. Quality of life (QOL) data from randomized studies trials of EGFR TKI and chemotherapy (C)

Study	Scales used	Completion rate of baseline assessment	Compliance with questionnaires	Symptom improvement
CTONG-0802 [13]	FACT-L, TOI, LCS	93%	TKI: 96/94/91% after cycle 2/4/6 respectively C: 100/82/50% after cycle 2/4/6, respectively	Improvement in FACT-L, TOI and LCS with erlotinib
LUX-Lung 3 [16]	EORTC QLQ-C30 and EORTC QLQ-LC13	97%	High (completion rate ≥ 90% throughout the study duration in both arms)	- Delay in time to deterioration in cough and dyspnea with afatinib. - Global health status/QOL and functional scales (physical, role, and cognitive) improve with afatinib.
LUX-Lung 6 [14]	EORTC QLQ-C30 and EORTC QLQ-LC13	NA*	TKI: 96% C: 88%	- Delay in time to deterioration in cough, dyspnea, and pain with afatinib. - Global health status/QOL and functional scales (physical, role, and social) improved with afatinib.
NEJ-002 [15]	Care Notebook	73%	TKI: 71% C: 75%	- Delay in time to deterioration in pain, shortness of breath, and daily function with gefitinib.

Abbreviations: EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire, EORTC QLQ LC13: QORTC QLQ lung cancer–specific module, FACT-L: Functional Assessment of Cancer Therapy-Lung (FACT-L), LCS: Lung Cancer Subscale, NA: not available, TOI: Trial Outcome Index

* A total of 290 (79.7%) patients among 364 randomized patients completed baseline and ≥ 1 post-baseline measurement.