Local Consolidation Therapy (LCT) After First Line Tyrosine Kinase Inhibitor (TKI) for Patients With *EGFR* Mutant Metastatic Non–small-cell Lung Cancer (NSCLC)

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Abstract

Despite an initial impressive response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), non–small-cell lung cancer (NSCLC) harboring TKI-sensitising EGFR mutations invariably acquire resistance after 9 to 14 months of TKI therapy. We have recently shown that the addition of local consolidation therapy (LCT) with surgery or radiation to standarad of care maintenance therapy improves progression-free survival in patients with molecularly unselected NSCLC. Herein, we retrospectively reviewed patients with EGFR mutant NSCLC treated with first-line TKI and LCT and found that their progression-free survival was 36 months compared with 14 months in patients treated with TKI alone. Our findings suggested that combining LCT with TKI may represent an effective therapeutic startegy in this subset of patients.

Introduction: Although most NSCLC patients with sensitizing epidermal growth factor receptor (*EGFR*) mutations have an impressive initial response, the vast majority has residual disease and develops acquired resistance after 9 to 14 months of EGFR tyrosine kinase (TKI) therapy. We recently reported a phase II trial showing that, for patients with molecularly unselected oligometastatic NSCLC who did not progress after first-line systemic therapy, local consolidation therapy (LCT) with surgery or radiation improved progression-free survival (PFS), compared with maintenance therapy alone. Herein, we report a retrospective analysis of LCT after TKI in patients with metastatic *EGFR* mutant NSCLC. **Patients and Methods:** We identified patients with metastatic *EGFR* mutant NSCLC treated with TKI plus LCT or with TKI alone in the MD Anderson GEMINI (Genomic Marker-Guided Therapy Initiative) database and in our recently published LCT trial. PFS was compared between LCT plus TKI and TKI only treated patients using the log-rank test. **Results:** We identified 129 patients with *EGFR* mutant NSCLC who were treated with first-line TKI and 12 that were treated with TKI followed by LCT. Among the 12 patients treated with TKI plus LCT, 8 patients had oligometastatic disease (defined as $\leq$ 3 metastases), and 4 patients had $>$ 3 metastases. LCT regimens were hypofractionated radiotherapy or stereotactic ablative body radiotherapy for 11 patients and surgery for 1 patient. TKI followed by LCT resulted in a significantly longer PFS (36 months) compared with TKI alone (PFS, 14 months; log-rank $P = .0024$). **Conclusions:** Our data suggests that first-line TKI plus LCT is a promising therapeutic strategy for patients with *EGFR* mutant NSCLC that merits further investigation.

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Introduction

Lung cancer continues to be the most common cause of cancer-related death worldwide, with a 5-year survival rate of less than 10% in patients with advanced disease.[1] Activating epidermal growth factor receptor (*EGFR*) mutations are key drivers of non−small-cell lung cancer (NSCLC) in 10% to 15% of patients of European descent and approximately 40% of patients of East Asian descent.[2] Treatment of this subset of patients with EGFR inhibitors is now standard of care, following demonstration of superiority over cytotoxic chemotherapy in phase III studies of erlotinib, gefitinib, and afatinib.[3-5]

Unfortunately, although approximately 55% to 70% of patients with sensitizing *EGFR* mutations (eg, L858R, Exon 19 deletion) have an objective tumor response, the vast majority develop acquired resistance after 9 to 14 months of EGFR tyrosine kinase inhibitor (TKI) therapy.[3-5] In an estimated 60% of these refractory cases, the cancer progression is driven by an additional gatekeeper *EGFR* mutation (T790M), which confers resistance to erlotinib, gefitinib, and afatinib.[6] Novel third-generation EGFR inhibitors that block both activating *EGFR* mutations (L858R and Exon 19 deletions) and T790M, such as osimertinib (AZD9291), elicit responses in approximately 60% of patients with *EGFR* mutant NSCLC with T790M-mediated resistance to their initial EGFR inhibitor.[7] Moreover, when compared with erlotinib or gefitinib in the first-line setting for EGFR mutant NSCLC, osimertinib showed a significant PFS benefit in favor of osimertinib in a phase III study.[7] However, similar to other EGFR inhibitors, many patients develop resistance to this agent as well. Clearly, more effective strategies to prevent resistance emergence are urgently needed.

Several retrospective and small prospective trials have suggested a benefit with local therapy in the setting of select metastatic disease, particularly oligometastases.[8,9] In this context, we recently conducted a multi-institutional, randomized, phase II study comparing the role of aggressive local consolidation therapy (LCT) in patients with $\leq$ 3 metastases who did not progress on standard front-line systemic therapy/observation.[10] Our hypothesis was that consolidative therapy would improve progression-free survival (PFS) in this setting. Appropriate front-line systemic therapy was defined as either $\geq$ 4 cycles of platinum doublet therapy or $\geq$ 3 months of EGFR/anaplastic lymphoma kinase (ALK) inhibitor for patients with *EGFR* mutations/*ALK* rearrangements, respectively. Patients were randomized to either LCT ([chemo]radiation or surgical resection of all sites) $\pm$ ongoing maintenance therapy/observation (MT/O) versus MT/O alone. The MT/O was physician choice (from predefined standard-of-care options). Forty-nine patients were randomized (25 in the LCT arm), 8 of whom had *EGFR*/*ALK* alterations. The median PFS in the LCT arm was 11.9 months, compared with 3.9 months in the no-LCT arm (hazard ratio [HR], 0.35; $P = .007$). Importantly, time to the appearance of a new lesion was longer among patients in the LCT group than among patients in the MT/O group (11.9 vs. 5.7 months; $P = .0497$).

Herein, we retrospectively review our recently published LCT clinical trial[10] and MD Anderson Cancer Center GEMINI (Genomic Marker-Guided Therapy Initiative) database, to determine the clinical outcomes of LCT after first-line TKI in patients with metastatic *EGFR* mutant NSCLC. Our hypothesis was that, similar to the findings in our recently published randomized phase II study, there would be a benefit in PFS with LCT when analyzing only patients that received first-line TKI agents.

Materials and Methods

This is a post-hoc analysis of our recently published phase II LCT clinical trial and a retrospective review of the MD Anderson Cancer Center GEMINI database, which is a prospectively collected database that includes patients' demographics, tumor molecular profiles, treatment history, and clinical outcomes.

Patients with a diagnosis of pathologically confirmed *EGFR* mutant NSCLC, stage IV disease according to the seventh edition of the American Joint Committee on Cancer staging system, treated with first-line TKI (erlotinib, gefitinib, or afatinib) without progression followed by LCT with surgery or radiation were identified (LCT plus TKI group). Patients who received LCT at the time of progression or oligoprogression were not included in the LCT plus TKI group Patients with stage IV *EGFR* mutant NSCLC treated with first-line TKI were identified (TKI-only group). Oligometastatic disease was defined as $\leq$ 3 metastatic lesions at the time of diagnosis, whereas polymetastatic disease was defined as $>$ 3 metastatic lesions at the time of diagnosis. Positive thoracic nodes (N1-N3) were counted collectively as 1 lesion. For the 2 groups, PFS was defined from the time of TKI start to progression or death, whichever occurred first. For patients who remained alive without evidence of cancer progression, the PFS date was censored at their last clinic follow-up. PFS was compared between the LCT plus TKI and TKI-only groups using the log-rank test. The study was approved by the institutional review board (MD Anderson Cancer Center IRB no. PA16-0061).

Results

In the GEMINI database, we identified 129 patients with *EGFR* (L858R, Exon 19 deletion, L861Q) mutant stage IV NSCLC treated with first-line TKI (TKI-only group) and 12 that were treated with TKI followed by LCT (3 treated within our recently published LCT clinical trial and 9 at the discretion of their physician). Patient characteristics of both groups are noted in Table 1. Among the 12 patients treated with TKI plus LCT, 8 patients had oligometastatic disease (defined as $\leq$ 3 metastases), and 4 patients had $>$ 3 metastases (Table 2). In contrast, 44 (34%) patients in the TKI-only group had oligometastatic disease, whereas 85 (66%) had $>$ 3 metastases.

Two of the 12 patients treated with TKI plus LCT had brain metastases at the time of diagnosis and were treated with brain radiation prior to commencement of first-line TKI, which was followed by LCT to a non-brain site. The results of the *EGFR* testing were not available at the time of initiation of therapy for 2 patients in the LCT plus TKI group, and hence, 1 patient received 2 cycles of carboplatin and pemetrexed, whereas the other received 1 cycle of carboplatin and pemetrexed before transitioning to a TKI once *EGFR* testing results became available. The median time on induction TKI (ie, prior to LCT) was 4 months (range, 2-15 months). LCT regimens were hypofractionated radiotherapy or stereotactic ablative body radiotherapy for 11 patients and surgery for 1 patient. The latter patient had segmentectomy of residual nodules in the upper and lower lobes of the left lung. All patients in the LCT plus

Table 1 Patient Characteristics

Characteristic	LCT + TKI, n (%)	TKI Alone, n (%)
Total patients	N = 12	N = 129
Age, y		
Median	54	63
Range	44-83	29-89
Gender		
Male	6 (50)	56 (43)
Female	6 (50)	73 (57)
Smoking history		
Never-smoker	10 (83)	92 (71)
Active/former	2 (17)	37 (29)
EGFR mutation type		
Exon 19 deletion	9	81
L858R	3	45
L861Q	-	3
Number of metastatic sites		
≤ 3 (oligometastatic)	8 (67)	44 (34)
> 3 (polymetastatic)	4 (33)	85 (66)
Patients with brain metastasis	2 (17)	32 (25)
Patients with extra-thoracic metastasis	6 (50)	49 (38)

Abbreviations: EGFR = Epidermal growth factor receptor; LCT = local consolidation therapy; TKI = tyrosine kinase inhibitors.

TKI group continued their TKI beyond LCT until progression. LCT was well-tolerated. One patient in the LCT plus TKI group had an uncomplicated pulmonary embolism. No patient in the LCT plus TKI group had grade 4 adverse events or died because of an adverse event.

Patients treated with LCT plus TKI had significantly longer PFS than patients treated with TKI only: the median PFS was 36 months in the LCT plus TKI group and 14 months in the TKI-only group (HR, 0.29; 95% confidence interval [CI], 0.23-0.70; log-rank $P = .0024$) (Figure 1). With a median follow-up in the LCT plus TKI group of 36 months, the median overall survival (OS) was not reached (range, 11 months to not reached) (Figure 2). To date, 5 patients in the LCT plus TKI group have progressed. Among the 5 patients who developed disease progression, the first sites of progression were new lesions in 3 patients (new sites were lung, bone, and brain; 1 patient each), and 1 patient had a new disease site (lung) as well as progression of previously irradiated lung lesion. The final patient had disease progression in previously irradiated chest lymph nodes. The median OS of the TKI-only group was 35 months. The difference in OS between the 2 groups did not reach statistical significance (log-rank $P = .06$).

Discussion

EGFR mutant NSCLC has a distinct clinical course characterized by an initial substantial response to EGFR TKI followed, inevitably, by acquired resistance to this class of agents. We recently reported that local consolidative therapy after initial systemic therapy was feasible, tolerable, and significantly extended PFS time compared with maintenance therapy or observation alone among patients with molecularly unselected oligometastatic NSCLC.

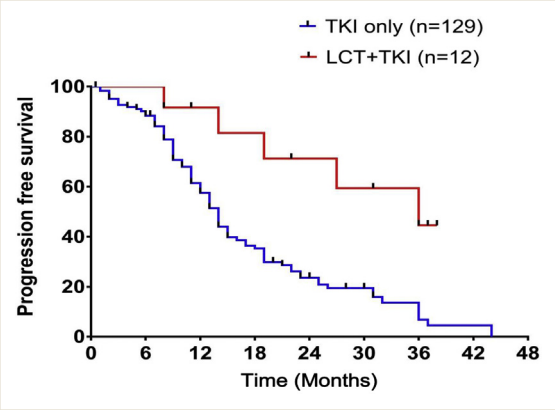
In the present study, we retrospectively reviewed our LCT clinical trial and the GEMINI database and found that patients who received an EGFR TKI and LCT had a longer PFS than those who had TKI alone (36 vs. 14 months; $P = .0024$). Our data should be interpreted with caution for several reasons. First, the study is retrospective and non-randomized. Secondly, in our GEMINI dataset that has more than 200 patients with *EGFR* mutant NSCLC, only 12 patients were treated with LCT plus TKI, suggesting that LCT may be used in a selected population. Finally, 8 of 12 patients treated with this approach had oligometasatic disease, which is likely to have a better prognosis. It is worth noting, however, that in the MT/O arm of our recently reported LCT trial, a median PFS of 3.9 months was observed from the time of randomization, consistent with the median PFS for the overall population with metastatic NSCLC.[10-12] Furthermore, the PFS observed in our EGFR TKI-alone arm (14 months) is consistent with prior larger clinical studies in patients with *EGFR* mutant NSCLC treated with an EGFR TKI.[3-5]

Table 2 Patients in the LCT + TKI Group: TKI, Metastatic Sites, and Procedures Performed

Patient	TKI	Metastatic Sites	LCT
1	Erlotinib	Bilateral pulmonary metastases, axillary and supraclavicular lymph nodes	SBRT to primary tumor and lymph nodes
2	Erlotinib	Thoracic lymph nodes and bone	RT to primary tumor and lymph nodes
3	Erlotinib	Thoracic lymph nodes and malignant pleural effusion	RT to primary tumor and lymph nodes
4	Erlotinib	Bilateral pulmonary metastases, multiple bone metastases	Left upper lobe and left lower lobe segmentectomy
5	Erlotinib	Thoracic lymph nodes and malignant pleural effusion	RT to primary tumor
6	Erlotinib	Humerus and metastatic pulmonary nodule	RT to primary tumor and humerus
7	Erlotinib	Thoracic lymph nodes and multiple bone metastases	RT to left iliac metastasis
8	Afatinib	Thoracic and contralateral supraclavicular lymph nodes	RT to primary tumor and thoracic lymph nodes
9	Gefitinib	Brain	RT to primary tumor and brain
10	Erlotinib	Thoracic lymph nodes and multiple pleural metastatic deposits	RT to primary tumor
11	Erlotinib	Three bilateral metastatic pulmonary nodules	RT to all 3 bilateral pulmonary nodules
12	Erlotinib	Thoracic lymph nodes and brain	RT to brain and primary tumor

Abbreviations: LCT = Local consolidation therapy; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

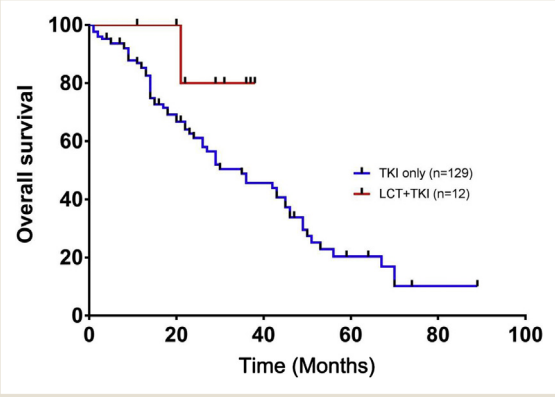
Figure 1 Progression-free Survival. TKI-only Group = 14 Months, TKI + LCT Group = 36 Months (HR, 0.29; 95% CI, 0.23-0.70; Log-rank *P* = .0024)



Abbreviations: CI = confidence interval; HR = hazard ratio; LCT = local consolidation therapy; TKI = tyrosine kinase inhibitors.

A previous retrospective study of patients with oligoprogressive NSCLC following EGFR TKI showed that local therapy with surgery, radiation, or radiofrequency ablation was associated with a median OS of 41 months, a median time to next systemic therapy of 22 months, and a median time to progression of 10 months.[13] Based on these results, local therapy of oligoprogressive *EGFR* mutant NSCLC on first-line TKI is being evaluated in a prospective clinical trial (NCT02759835). This approach differs from LCT described here and in our earlier study[10] in the timing of the local therapy, as LCT was given for non-progressing patients after initial systemic therapy. One potential advantage of ablating residual disease in non-progressing patients, instead of oligoprogressive patients, is that it may delay or prevent the emergence of resistant clones before additional metastatic spread occurs, as suggested by the observation that LCT delays the time to new metastases.[10] Nevertheless, the optimal timing of local therapy, and the optimal patient population (eg, oligometastic vs. polymetastatic disease) remain important unanswered questions.

Figure 2 Median Overall Survival. TKI-only Group = 35 Months. TKI + LCT Group = Not Reached (Range, 11 to Not Reached) (HR, 0.29; 95% CI, 0.13-0.66; Log-rank *P* = .06)



Abbreviations: CI = confidence interval; HR = hazard ratio; LCT = local consolidation therapy; TKI = tyrosine kinase inhibitors.

Conclusion

In summary, our analysis shows that patients with *EGFR* mutant NSCLC tolerated LCT without obvious adverse events and had a promising PFS of 36 months compared with the control group treated with TKI alone of 14 months. Although this study has limitations of being retrospective and non-randomized, this profound difference in PFS, coupled with other studies of LCT and local treatment of oligoprogressive disease, suggest that the approach of aggressive local treatment warrants further investigation in a prospective randomized study. A multicenter phase II randomized trial comparing osimertinib plus LCT with osimertinib alone has recently started enrollment (NCT03410043).

Clinical Practice Points

- Patients with TKI-sensitizing EGFR mutations acquire resistance in 9 to 14 months; more effective treatment strategies are required.
- Our retrospective series from a phase II randomized trial and MD Anderson Cancer Center database shows that combining LCT with surgery or radiation with TKI leads to significant improvement in PFS compared with TKI alone.
- The addition of LCT to standard of care first-line TKI may be an effective therapeutic strategy. A prospective, randomized, multicenter phase II trial is testing this hypothesis (NCT03410043).

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Disclosure

The authors have stated that they have no conflicts of interest.

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