Editorial Commentary

Neoadjuvant therapy in localized non-small cell lung cancer: can we do better than chemotherapy?

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The oncologic importance of an epidermal growth factor receptor (EGFR) mutation in the era of tyrosine-kinase inhibitors (TKIs) for patients with metastatic non-small cell lung cancer (NSCLC) cannot be overstated. The multiple positive trials evaluating gefitinib, erlotinib, and more recently osimeritinib as first line treatment of EGFR mutated NSCLC have revolutionized NSCLC management, with significantly improved oncologic and toxicity outcomes in this subset of patients (1-3). However, use of EGFR-TKIs in the management of non-metastatic NSCLC has not been proven as of yet. Currently, patients with non-metastatic disease do not have any indications for EGFR-TKI outside of a clinical trial setting, with traditional chemotherapy given adjuvantly and neoadjuvantly around surgical resection, and concurrently with radiation therapy (4).

Zhong *et al.* recently published anticipated results from the EMERGING-CTONG 1,103 multicenter, randomized phase II trial, which explored the use of erlotinib (TKI) *vs.* gemcitabine plus cisplatin (GC) chemotherapy in the neoadjuvant/adjuvant setting for stage IIIA–N2 resectable NSCLC (5). Patients were randomly assigned to receive 6 weeks of neoadjuvant TKI, given daily, or GC, given every 3 weeks. Following surgery, patients received additional TKI therapy for up to 12 months or GC for an additional 2 cycles. Patients were deemed to have resectable N2 disease if the short-axis diameter was less than 3 cm and if there was no evidence of bulky or fixed lymph nodes. The primary endpoint was objective response rate (ORR), defined as either complete or partial response per the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Secondary end points included pathologic complete response, rates of pathological nodal downstaging (from N2 to N1 or N0), progression-free survival (PFS), overall survival (OS), safety, and tolerability.

Baseline characteristics were not evaluated for potentially statistically significant differences. There were numerically higher rates of T-classification ≥2 (85.7% *vs.* 64.8%), but lower rates of multi-station N2 disease (45.7% *vs.* 54.1%) in the GC arm. In total, 31/37 (83.8%) TKI and 24/35 (70.6%) GC patients were able to undergo surgery. No patients had a pathologic complete response. Rates of R0 resection were 73% and 63% for the TKI and GC arms respectively (P=NS). Lymph node downstaging occurred in 10.8% and 2.9% for the TKI and GC cohorts respectively (P=NS).

Out of 72 patients evaluated, the study found no significant difference in the primary endpoint of ORR (54.1% in TKI group *vs.* 34.3% in GC group, P=0.092). However, there was a significant increase in PFS in patients treated with TKI versus patients treated with GC chemotherapy (median PFS 21.5 *vs.* 11.4 months, P<0.001). This may have been driven by the planned difference in length of adjuvant therapy, as most patients in both arms received adjuvant therapy (75.7% for TKI, 62.9% for GC), but median duration of adjuvant TKI was 12 months, while GC was given for an additional 2 cycles. OS was similar between the two arms (45.8 months for TKI *vs.* 39.2 for GC, P=0.42). As expected, neoadjuvant TKI was better tolerated than GC (Grade 3+ toxicities 0% *vs.* 29.4%). In general, adverse events correlated with the known toxicity profiles of the two regimens, with increased skin toxicity associated with Erlotinib and more hematologic and

gastrointestinal toxicities associated with GC.

The results of this trial are certainly interesting but require framing in an appropriate context to optimize patient management. The lack of evaluation of potential statistically significant differences between the two groups at baseline may have led to confounding variables affecting some of the outcomes. The lack of a statistically significant benefit in ORR is likely driven by lack of sample size (rather than a true lack of benefit) in this phase II trial without adjustment to the alpha threshold of statistical significance, especially given the 20% absolute increase in ORR seen in this cohort, which is clinically meaningful. The discordant results of no difference in ORR at time of surgery but a significant PFS benefit is likely driven by the extended duration of adjuvant TKI, and additional follow-up is required to determine if this will manifest to an OS benefit with additional follow-up. This trial provides promising evidence that treating stage IIIA–N2 patients with erlotinib and surgical resection shows promise as a neoadjuvant and adjuvant therapy strategy in patients with EGFR mutated NSCLC.

Stage IIIA–N2 NSCLC patients have a multitude of treatment options, including definitive chemoradiation with consolidative durvalumab, induction chemoradiation followed by surgery, or induction chemotherapy followed by surgery and adjuvant radiation therapy when indicated (4,6-8). The ability to potentially use an oral medication which is a less toxic and more convenient form of systemic therapy that can have an effective ORR to improve surgical outcomes is highly desirable. However, a pathological nodal downstaging of 10% with erlotinib as seen in the study is less than ideal, given its importance in predicting rates of recurrence and OS (9-13). Additionally, whether postoperative radiation was utilized was not reported and may be an important factor in differentiating outcomes in one study (9). Regardless of these limitations, the study adds to the growing body of evidence demonstrating the potential benefit of routine testing of EGFR and other targetable mutations even in the non-metastatic NSCLC patient population (14). As the authors suggest, future studies are drastically needed to evaluate the role of targeted agents such as EGFR inhibitors, anaplastic lymphoma kinase (ALK) inhibitors, and programmed death-ligand 1 (PD-L1) inhibitors for example, in the setting of non-metastatic NSCLC given how impactful they have been in the metastatic cohort.

Another area of strong interest is the utilization of erlotinib or other TKIs concurrently with chemoradiation in stage IIIA-N2 disease. Several studies support the use of erlotinib as a concurrent therapy to chemoradiation in patients with locally advanced NSCLC. They found that adding erlotinib to chemoradiation or radiation therapy alone has a favorable safety profile and correlates with promising progression-free and overall survival rates (15,16). However, randomized phase II/III data is required in this clinical scenario as well in order to drive a paradigm shift in treatment and confirm the role of TKIs in the non-metastatic scenario. Lastly, there is some early evidence suggesting a positive role for TKIs such as gefinitib in early stage NSCLC (17).

Several ongoing clinical trials are testing the efficacy, safety, and timing for use of TKIs with chemotherapy, radiation, or both in NSCLC (Clinicaltrials.gov ID#: NCT00888511, NCT01573702, NCT02859077, NCT02759835, NCT01573702, NCT02759835). These clinical trials are paving the way for the use of erlotinib and other TKIs in treatment for non-metastatic NSCLC. The EMERGING-CTONG 1103 is the start of multiple positive studies liking to come forward in the next decade and offer more tailored therapy for EGFR positive NSCLC patients.

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Footnote

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