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Induction EGFR tyrosine kinase inhibitors prior to definitive chemoradiotherapy in unresectable stage III EGFR-mutated non-small cell lung cancer

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ABSTRACT

Introduction: Increasing evidence suggests that consolidation durvalumab confers limited benefits for patients with stage III *EGFR*-mutated NSCLC. Induction or maintenance EGFR tyrosine kinase inhibitors (TKIs) added to concurrent chemoradiotherapy (CRT) may optimize definitive treatment, but there are limited data supporting an induction TKI strategy.

Methods: We evaluated the efficacy and safety of induction EGFR TKIs administered before concurrent CRT in a retrospective series of patients with unresectable locally advanced *EGFR*-mutated NSCLC. Circulating tumor DNA (ctDNA) analysis was performed on a patient subset using CAPP-seq and correlated with outcomes.

Results: Of six patients, three received erlotinib and three osimertinib as induction therapy before CRT. Induction TKIs were administered for a median of 2.5 months. The objective response rate after induction TKI was 83%. One patient had a complete response to induction erlotinib and continued erlotinib for 4 years until local progression, which was treated with CRT. Two patients completed maintenance erlotinib after CRT, and another received consolidation durvalumab. After a median follow-up of 20.5 months, only one patient developed disease recurrence, with rising ctDNA coinciding with recurrence. ctDNA remained undetectable in patients without recurrence, or low-level in a patient receiving maintenance erlotinib. Adverse events were mild and expected, and none developed pneumonitis.

Conclusion: Induction EGFR TKI before CRT may achieve high disease control rates with promising signs of durability in patients with locally advanced *EGFR*-mutated NSCLC. ctDNA analysis after CRT can correlate well with clinical outcomes. Prospective studies are needed to define the role of induction EGFR TKIs in this setting.

Introduction

Locally advanced NSCLC occurs in one-third of patients and remains a challenging disease to cure. The standard of care for unresectable stage III NSCLC involves concurrent chemoradiotherapy (CRT) followed by consolidation durvalumab based on the positive results of the phase III PACIFIC trial [1]. However, accumulating evidence suggests that patients with *EGFR*-mutated NSCLC attain limited benefits from durvalumab and are at risk of immune-related adverse events [2]. At the five-year analysis of the PACIFIC trial, in a small subgroup analysis of patients with *EGFR*-mutated NSCLC, consolidation durvalumab showed early signals of a lack of benefit when compared with placebo in both

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progression-free survival (PFS) and overall survival [3]. We subsequently demonstrated in a multi-institutional retrospective analysis that PFS does not significantly differ between CRT with durvalumab and CRT alone (P=0.993) [2]. Several retrospective analyses have also emerged that show inferior PFS outcomes with durvalumab in driver-mutation positive NSCLC [4–6]. Thus, alternative approaches for definitive treatment of patients with unresectable locally advanced *EGFR*-mutated NSCLC merit investigation.

The role of EGFR tyrosine kinase inhibitors (TKIs) in enhancing outcomes of early-stage *EGFR*-mutated NSCLC has gained traction. Osimertinib, a third-generation EGFR TKI, is now available as adjuvant therapy for surgically-resected *EGFR*-mutated NSCLC based on the phase III ADAURA trial [7]. In patients with stage IB-IIIA disease, adjuvant osimertinib conferred an 80% reduction in the risk of recurrence compared with placebo, and appeared to attain higher relative risk reductions among patients with later stages of disease. Additionally, the phase III NeoADAURA trial is assessing neoadjuvant osimertinib for resectable *EGFR*-mutated NSCLC (NCT04351555) [8]. For unresectable stage III *EGFR*-mutated NSCLC, the phase III LAURA trial will investigate osimertinib after CRT compared with placebo (NCT03521154). However, there are limited data evaluating induction EGFR TKIs administered before CRT.

Here, we present a series of patients with stage III *EGFR*-mutated NSCLC who received induction EGFR TKIs, specifically osimertinib and erlotinib, before CRT. We evaluated the efficacy and safety of this approach and its correlation with measures of circulating tumor DNA (ctDNA) in a patient subset.

Materials and methods

Study design

In this single-institution retrospective analysis completed at the Stanford Cancer Institute, we identified all patients with unresectable stage III or locally advanced recurrent *EGFR*-mutated NSCLC who received an induction EGFR TKI and completed concurrent CRT from April 2011 to July 2020, with a data cutoff of February 2021. Induction EGFR TKIs were administered off-label per the treating physician's standard practice. Patients were permitted to receive adjuvant therapy after CRT—such as maintenance EGFR TKI or consolidation chemotherapy or durvalumab—at the treating physician's discretion. *EGFR* molecular testing was performed at diagnosis using a next-generation sequencing (NGS) panel [9,10] or targeted gene assays. This analysis was conducted under two institutional review board (IRB)-approved protocols (NCT01385722 and NCT00349830).

Demographic, clinical, and pathologic data were abstracted from electronic health records. NSCLC histology was classified based on the World Health Criteria criteria [11]. Disease staging conformed to the eighth edition of the American Joint Committee on Cancer and International Union Against Cancer TNM stage classification for lung cancer [12].

Outcomes

Tumor responses following induction EGFR TKI were assessed before the initiation of CRT using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [13]. Disease recurrence was evaluated using RECIST version 1.1 criteria. Time to recurrence was measured from the date of CRT completion to the date of recurrence if it occurred or censored at last follow-up. Adverse events (AEs) were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

ctDNA analysis

Plasma samples were prospectively collected for ctDNA analysis from four patients (Patient No. 1-3 and 5), around the time of treatment with CRT for three patients (Patient No. 1, 2, and 5) and during the maintenance TKI period for one (Patient No. 3) as part of an IRB-approved biorepository at Stanford University (NCT00349830). Collection of samples occurred at the initiation and conclusion of treatment with CRT and then at timepoints that coincided with imaging. Samples were retrospectively queried for the presence of minimal residual disease (MRD), or small amounts of remnant tumor cells, using a tumor-informed approach through the CAncer Personalized Profiling by deep sequencing (CAPP-seq) method, as previously described [9,14]. Briefly, baseline molecular genotyping of tumor issue identified mutations present at initial diagnosis which were then evaluated for during subsequent collections of plasma samples following treatment. This approach achieves an increased sensitivity compared with a tumor genotype-naïve approach, whereby a widespread screen for ctDNA is conducted without *a priori* knowledge of the baseline tumor mutations [15].

At each timepoint, the detection of ctDNA, and presence of MRD, was determined through a Monte Carlo-based ctDNA detection index cutoff point of $\leq$0.05, as previously established [9,14]. If the ctDNA detection index was >0.05, ctDNA was classified as not detected; if it was $\leq$0.05, ctDNA was classified as detected at a given timepoint. The ctDNA-mutant allele frequency (AF) at each timepoint was calculated by averaging the mutant AFs for all mutations used in the detection process. ctDNA concentration was determined by multiplying the mutant AF by the cell-free DNA concentration as measured by Qubit (ThermoFisher Scientific), with the assumption that each haploid genomic equivalent weighs 3.3 picograms.

Results

Patient characteristics

Six patients received induction EGFR TKI before CRT. Median age at EGFR TKI initiation was 65.0 years, five patients were female, and three had a former smoking history (Table 1). Two patients had stage IIIA and four had stage IIIB disease, with five having lung adenocarcinoma and one with a lung adenosquamous carcinoma. Three patients had *EGFR* exon 19 deletions, two *EGFR* L858R, and one *EGFR* L861Q. Co-occurring mutations were evaluable in four patients and most commonly include *TP53* mutations.

Induction erlotinib

Three patients received induction erlotinib before CRT (Table 1, Fig. 1). Patient No. 1 received induction erlotinib for 0.8 months. She presented with a 1.0 cm right upper lobe (RUL) nodule and a 4.2 cm right suprahilar mass invading the lower lobe and right mainstem bronchus, which increased to 4.8 cm on follow-up imaging, resulting in partial obstruction. She had a stent placed in the right mainstem bronchus and terminated induction therapy early for CRT with carboplatin/pemetrexed. Following CRT, she did not receive any further consolidation treatment. After 33.4 months of follow-up, she remains without evidence of disease recurrence. ctDNA analysis was performed on the patient's plasma samples (Fig. 2A), with detectable ctDNA measured at the end of induction erlotinib and at midpoint during CRT, suggesting evidence of MRD. ctDNA was cleared at the end of CRT and remained undetectable throughout follow-up, which correlated with the patient's lack of radiographic progression.

Patient No. 2 presented with a 4.6 cm right infrahilar mass representing confluent lymphadenopathy extending to the subcarinal space. She initiated induction erlotinib, achieving a complete response. In the absence of visualizable tumor, CRT was held in favor of ongoing erlotinib. After nearly 4 years, she developed a right lower lobe (RLL) nodule at the original site of disease, biopsy-proven as recurrent adenocarcinoma. Following 2 years of slow progression, she completed CRT with

Table 1
Patient characteristics.

Patient No.	Clinical Age[a], Sex, Smoking Status	Stage[b]	Histology	*EGFR* Mutation	Co-mutations	Induction EGFR TKI Duration (mo)	Induction EGFR TKI Tumor % Change	RECIST Response	Concurrent CRT CRT Regimen	Consol. Chemo	Other Consol.	Follow-up after CRT (mo)
Induction Erlotinib												
1	82, F, Never	IIIA, T4N0	Adenocarcinoma	L858R	$TP53^{MUT}$, $TP63^{MUT}$, $FGFR2^{MUT}$	0.8	11.5	PD[c]	Carboplatin/ pemetrexed	No	No	33.4
2	34, F, Never	IIIB, T4N2	Adenocarcinoma	Exon 19 deletion	$TP53^{MUT}$	73.8	-100.0	CR	Cisplatin/ pemetrexed	No	Maintenance erlotinib	6.3 (progression)
3	63, F, Former	IIIB, T2N3	Adenocarcinoma	L861Q	$TP53^{MUT}$	2.1	-43.2	PR	Cisplatin/ etoposide	Yes	Maintenance erlotinib	118.0
Induction Osimertinib												
4	69, F, Never	IIIB, T2N3	Adenocarcinoma	Exon 19 deletion	NE	2.9	-75.0	PR	Cisplatin/ pemetrexed	No	No	13.7
5	66, F, Former	IIIA, rT2N2	Adenocarcinoma	Exon 19 deletion	None	7.6	-35.3	PR	Carboplatin/ pemetrexed	Yes	No	27.3
6	64, M, Former	IIIB, T3N2	Adenosquamous	L858R	NE	1.9	-79.6	PR	Carboplatin/ paclitaxel	No	Durvalumab	7.4

Abbreviations: *No.* number, *TKI* tyrosine kinase inhibitor, *CRT* chemoradiotherapy, *RECIST* Response Evaluation Criteria in Solid Tumors v1.1, *Consol.* Consolidation, *F* female, *PD* progressive disease, *CR* complete response, *PR* partial response, *NE* not evaluable, *r* recurrent, *M* male.

[a] Age (years) reported at initiation of induction EGFR TKI.

[b] Disease stage was classified according to the American Joint Committee on Cancer 8th edition of the TNM Staging System.

[c] Patient was classified as having progressive disease given the bronchial collapse from the tumor growth.

cisplatin/pemetrexed, then resumed maintenance erlotinib. She unfortunately had disease recurrence after 6.3 months of follow-up, and initiated palliative systemic therapy with pembrolizumab. ctDNA analysis was performed during CRT and at the first follow-up imaging timepoint with undetectable levels (Fig. 2B). Imaging at this first follow-up timepoint with both high-resolution computed tomography (CT) and positron emission tomography (PET)/CT revealed no evidence of local recurrence or lymphadenopathy and showed a complete metabolic response to CRT. At the second follow-up timepoint during at the administration of maintenance erlotinib, radiographic disease recurrence with sub-centimeter (2-7 mm) bilateral pulmonary nodules was observed and coincided with rising ctDNA levels, with further increases noted until the time of progression with next-line pembrolizumab.

Patient No. 3 presented with a 4.8 cm RUL mass and extensive lymphadenopathy in the supraclavicular and low cervical regions. Of note, her tumor harbored the atypical *EGFR* L861Q mutation (Table 1). She completed 2.1 months of induction erlotinib and achieved a partial response with a 43.2% reduction in tumor burden. The patient completed CRT with cisplatin/etoposide, with radiation targeting all original sites of disease, followed by consolidation chemotherapy. Subsequently, she initiated maintenance erlotinib, given her borderline metastatic disease. ctDNA analysis was performed during the maintenance erlotinib period, with the initial draw occurring after nearly 6 years of maintenance therapy. This initial timepoint measured detectable ctDNA, suggestive of MRD (Fig. 2C). Repeat ctDNA analyses six months and then one year later were both negative. After an additional year, MRD was again detected on ctDNA analysis. Given the patient's ongoing radiographic control and the treatment's excellent tolerability, maintenance erlotinib was continued indefinitely. After nearly 10 years, there has been no evidence of radiographic disease recurrence.

Induction osimertinib

Three patients received induction osimertinib before CRT (Table 1, Fig. 1). Patient No. 4 presented with a 2.0 cm left upper lobe nodule with extensive lymphadenopathy extending to the supraclavicular regions. She initiated 2.9 months of induction osimertinib, achieving a partial response with a 75.0% decrease in tumor burden. The patient completed CRT with cisplatin/pemetrexed, and remained disease-free after 13.7 months of follow-up.

Patient No. 5 presented with a 3.0 cm pT2aN2 RLL mass for which she completed a lobectomy with adjuvant cisplatin/vinorelbine, and post-operative radiation to the surgical bed. Seven years later, she developed biopsy-confirmed recurrence to a right supraclavicular lymph node, measuring 1.7 cm short axis. Induction osimertinib was initiated, achieving a 35.3% partial reduction. The patient underwent CRT with carboplatin/pemetrexed followed by consolidation chemotherapy. There was no evidence of recurrence after 27.3 months of follow-up. ctDNA analysis was performed near the end of induction osimertinib, with detectable ctDNA suggesting evidence of MRD (Fig. 2D). ctDNA was undetectable at the initiation and completion of CRT, and remained undetectable in the initial timepoints that were evaluated during follow-up, which correlated with the patient's lack of radiographic progression.

Patient No. 6 presented with a left-sided 5.4 cm Pancoast tumor and lymphadenopathy in the AP window. He initiated induction osimertinib for 1.9 months and attained a partial response with a 79.6% decrease in tumor size. He completed CRT with carboplatin/paclitaxel followed by 13 cycles of consolidation durvalumab without recurrence by the end of study follow-up.

Overall efficacy and safety

Altogether, the six patients completed induction EGFR TKIs for a median of 2.5 months (Table 1, Fig. 1). The objective response rate (ORR) after induction EGFR TKI was 83% (Fig. 3). After a median follow-up of 20.5 months, one developed disease recurrence. Rash

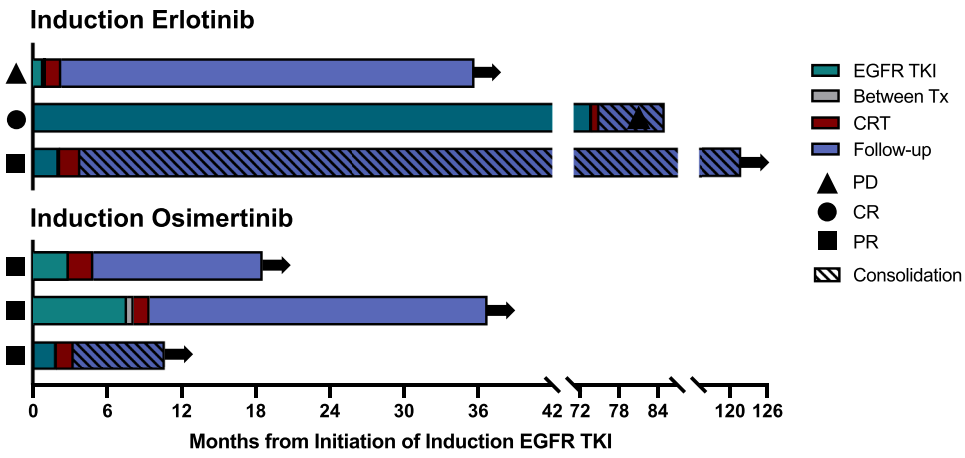

Fig. 1. Swimmers plot of patients receiving induction EGFR tyrosine kinase inhibitor and concurrent chemoradiotherapy.
Objective responses of induction EGFR TKI by Response Evaluation Criteria in Solid Tumors v1.1 criteria are indicated by the black triangle (progressive disease), black circle (complete response), and black square (partial response). Black arrows indicate ongoing follow-up without recurrence. Consolidation therapies included maintenance erlotinib (second and third patients under induction erlotinib) and durvalumab (third patient under induction osimertinib). Abbreviations: *TKI* tyrosine kinase inhibitor, *Tx* treatment, *CRT* chemoradiotherapy, *PD* progressive disease, *CR* complete response, *PR* partial response.

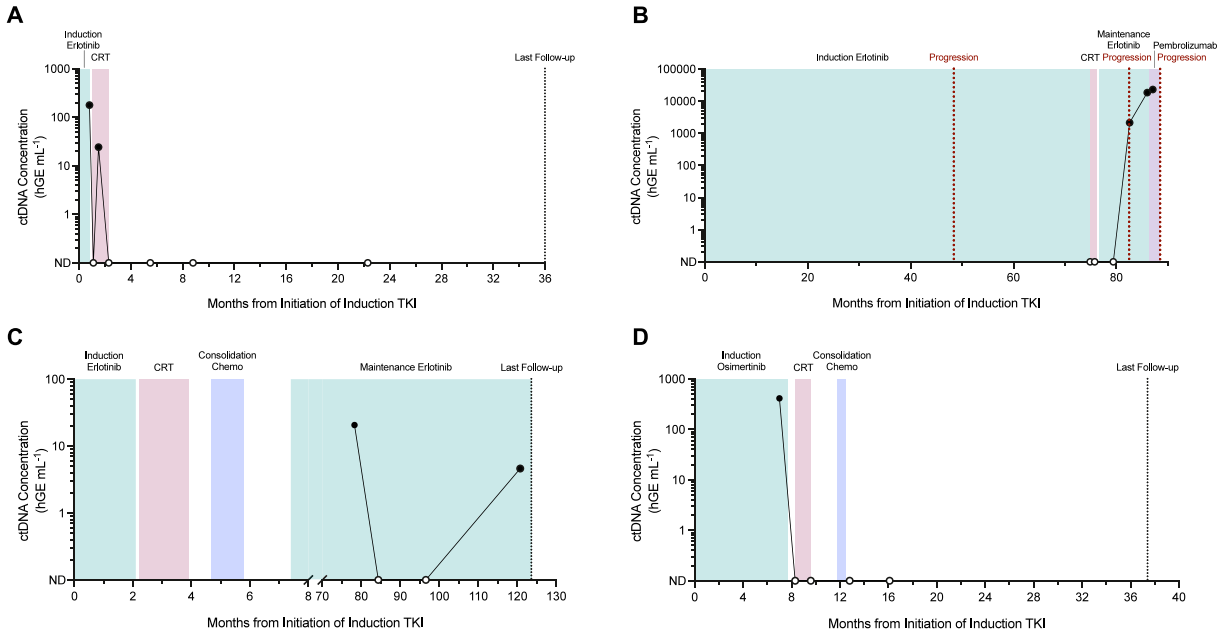

Fig. 2. ctDNA analysis.
ctDNA concentrations during and after completion of concurrent chemoradiotherapy were measured on a subset of patients with available plasma samples and correlated with clinical outcomes. Measurements for Patient No. 1 are depicted in panel (A), for Patient No. 2 in panel (B), for Patient No. 3 in panel (C), and for Patient No. 5 in panel (D). Abbreviations: *ctDNA* circulating tumor DNA, *No.* number, *hGE* haploid genome equivalent, *mL* milliliters, *ND* not detected, *TKI* tyrosine kinase inhibitor, *CRT* chemoradiotherapy.

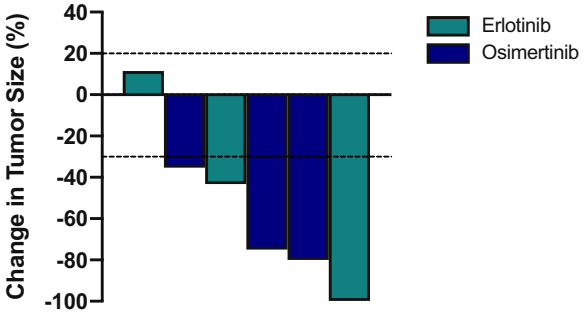

Fig. 3. Maximal change in tumor size with induction EGFR tyrosine kinase inhibitor.
Changes in tumor size were measured based on Response Evaluation Criteria in Solid Tumors v1.1 criteria at the first radiographic timepoint at the conclusion of induction EGFR tyrosine kinase inhibitor therapy.

(grade 1 and 2) and diarrhea (grade 1) were the most common AEs with induction EGFR TKI (Fig. 4). Grade 3 AEs occurred in four patients during CRT only, and included anemia, leukopenia, increased alanine transaminase, and dysphagia associated with esophagitis. All grade 3 AEs were transient and resolved with CRT completion. None developed pneumonitis during induction EGFR TKI, CRT, or afterwards.

Discussion

In this case series, we demonstrate that induction EGFR TKI before concurrent CRT can substantially reduce the tumor burden in patients with unresectable stage III *EGFR*-mutated NSCLC with encouraging recurrence-free survival and safety signals. One benefit of this approach is the possibility of shrinking the radiation field–especially important for Patients No. 3 and 4 who presented with extensive lymphadenopathy—that may make the tumor burden more amenable to definitive CRT. Induction EGFR TKI can also treat undetected micrometastases [8],

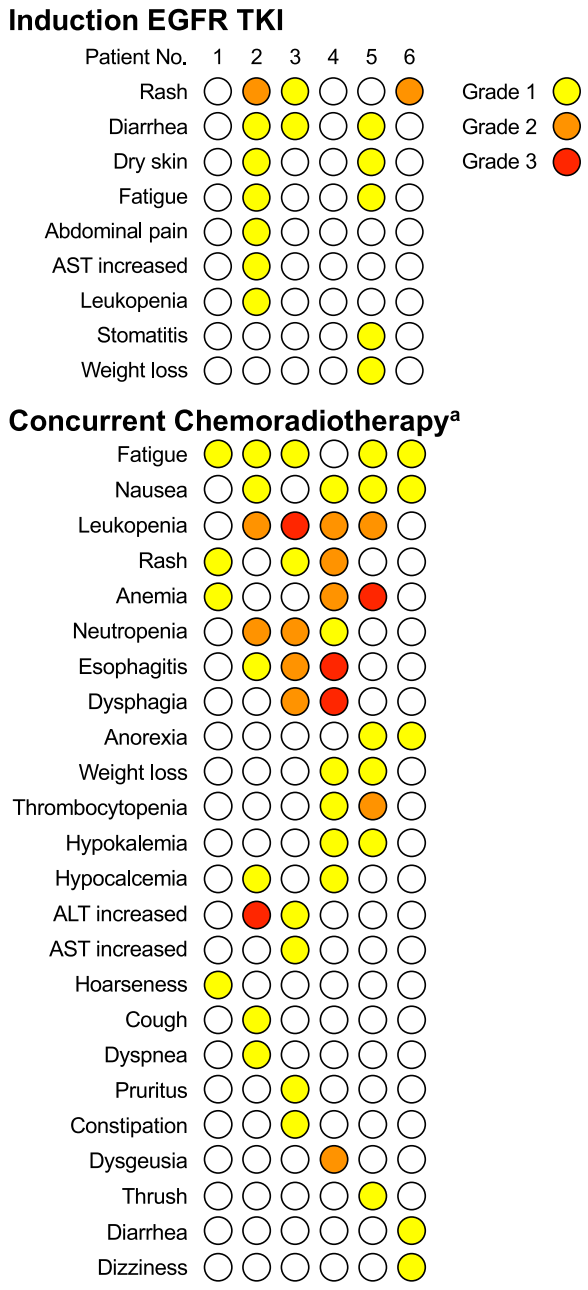

Fig. 4. Adverse events during induction EGFR TKI and concurrent chemoradiotherapy.

Adverse events were graded based on the Common Terminology Criteria for Adverse Events version 5.0. Each column represents a single patient. Abbreviations: *TKI* tyrosine kinase inhibitor, *No.* number, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase.

[a] Patient No. 4 who experienced grade 3 esophagitis/dysphagia was treated to a high total dose of radiotherapy at an outside institution and the adverse events were believed unlikely related to induction EGFR TKI therapy; dosimetric details were unavailable.

and the use of a third-generation EGFR TKI such as osimertinib can offer excellent penetration into the brain [16,17], which is critical given the frequent brain recurrence observed in patients with *EGFR*-mutated NSCLC [18,19]. After CRT, consolidation chemotherapy can be completed without interruption, though further studies will need to assess the role of maintenance EGFR TKI with this approach. In this series, Patients No. 1, 4, and 5 completed CRT without maintenance EGFR TKI and achieved lasting recurrence-free survival. In case of recurrence, these patients would likely be rechallenged with EGFR TKI as first-line therapy. Others, similar to Patient No. 3, may benefit from ongoing maintenance EGFR TKI, and predictive biomarkers, such as ctDNA analysis evaluating for MRD, might help to guide these treatment decisions.

The utility of ctDNA MRD detection has been previously examined in the locally advanced NSCLC setting. In a retrospective analysis of 40 patients with early-stage lung cancer, of whom 18 had locally advanced NSCLC treated with concurrent CRT, ctDNA was evaluated via a tumor-informed approach at both a prespecified posttreatment landmark timepoint and across multiple sequential posttreatment timepoints under surveillance analysis [20]. Through both strategies, the presence of detectable ctDNA correlated with eventual disease progression. In the ctDNA landmark analysis, the clinical sensitivity was 94% and specificity 100%, and in the ctDNA surveillance analysis, the clinical sensitivity was 100% and specificity 100%. A separate study of 65 patients with unresectable stage IIB-IIIB NSCLC (59 with stage III disease), all of whom received concurrent CRT, described outcomes with and without consolidation immunotherapy based on the presence of posttreatment ctDNA MRD [21]. Among those who were negative for ctDNA MRD at the posttreatment landmark, the administration of consolidation immunotherapy did not improve freedom from progression (FFP). However, among patients with detectable ctDNA MRD at the posttreatment landmark, consolidation immunotherapy was associated with a significant improvement in FFP, suggesting a potential role for consolidation therapy specifically among patients with evidence of MRD after standard definitive CRT.

To our knowledge, this is the first report to cross-examine ctDNA levels with outcomes in patients with *EGFR*-mutated NSCLC after induction EGFR TKI therapy followed by CRT. We found that undetectable ctDNA at the completion of CRT and at subsequent follow-up timepoints correlated with the absence of radiographic disease recurrence in Patients No. 1 and 5, even without the administration of maintenance EGFR TKI therapy. Patient No. 2's post-CRT ctDNA levels corresponded with what was observed radiographically, with undetectable ctDNA at the first follow-up timepoint coinciding with a lack of radiographic disease recurrence, and subsequently increasing ctDNA that aligned with the emergence of subcentimeter bilateral pulmonary nodules. Further increases in ctDNA concentration corresponded with ongoing radiographic progression. Ideally, a rising ctDNA concentration would have preceded the development of radiographic recurrence, as often occurred in a prior analysis [20]. This might have supported the addition of cytotoxic chemotherapy to the maintenance regimen or prompted a switch in systemic therapy altogether if there was concern for coincident clinical progression, although such strategies would be considered investigational. It is possible that the ctDNA assay was unable to capture low levels of post-CRT ctDNA, and this might be ameliorated with the use of higher sensitivity assays such as PhasED-seq [22]. Patient No. 3 had samples available for ctDNA analysis only during the maintenance erlotinib period, but even these were informative. Two out of the four timepoints showed low levels of detectable ctDNA, suggesting that MRD may be present despite the patient's negative imaging. Ongoing maintenance erlotinib might be contributing to disease control, which was longer than expected and potentially due to the combination of CRT with induction and maintenance erlotinib. After discussing the investigational nature of this analysis, and considering the patient's ongoing radiographic response and excellent treatment tolerability, the patient and treating physician agreed to continue maintenance erlotinib for the time being.

This series highlights a few treatment scenarios to consider in the design of clinical trials evaluating induction EGFR TKIs and the implementation of this strategy into clinical practice. Patient No. 2 received induction erlotinib with the plan to complete three months of induction therapy. At the time of post-induction imaging, a complete response was noted. In this case, in the absence of visualizable tumor, the patient and treating physician elected to continue erlotinib. An alternative option

could have been to pursue concurrent CRT targeted to the previous tumor site. Unfortunately, there are no data to guide this decision, as previous studies that evaluated response to induction chemotherapy before CRT did not achieve a complete response [23,24]. The opposite scenario may also arise with progression occurring during induction EGFR TKI therapy. In this series, Patient No. 1 experience clinical progression during induction erlotinib. In this case, induction therapy was terminated early and CRT commenced. Despite the early progression, the patient did not experience disease recurrence following CRT (and without maintenance EGFR TKI), suggesting a potential "salvage" role for CRT in this context. Another scenario that could arise, which was not demonstrated in the present cohort, is the identification of distant metastasis after induction EGR TKI that were not visualized during baseline radiographic imaging. One example is the presence of bone metastases, which, if small, can be missed with initial imaging, but often sclerose following treatment with EGFR TKIs and can, thus, become evident after repeat imaging. In this case, a patient would consequently be reclassified as having stage IV disease, and concurrent CRT could still be pursued for debulking purposes but would likely need to be followed by ongoing EGFR TKI therapy for systemic disease control. All the above scenarios would warrant individually tailored discussions between patient and physician weighing the risks and benefits between approaches given the lack of evidence for guiding these treatment decisions.

Few data exist on the induction EGFR TKI and concurrent CRT approach for stage III *EGFR*-mutated NSCLC. The phase II RTOG-1306 trial investigated induction erlotinib hydrochloride for 12 weeks followed by CRT (NCT01822496), but terminated early due to slow accrual. Another phase II trial evaluated induction gefitinib for 8 weeks followed by CRT among 20 patients, achieving an ORR of 90% in the induction phase and a 90% 2-year overall survival [25]. In the phase II ASCENT trial, induction afatinib was administered for two months followed by CRT +/- surgery [26]. Nineteen patients achieved an ORR of 58% and a median PFS of 34.6 months. Notably, 55% of patients with recurrent disease experienced central nervous system-only recurrence, highlighting the need to assess the role of brain-penetrant EGFR TKIs, such as osimertinib.

Limitations of this analysis include a small sample size, variations in the induction EGFR TKI and consolidation therapy approaches, and the retrospective assessment of outcomes. While the ctDNA analysis was informative in correlating with outcomes after CRT, unfortunately we did not have pre- and post-induction EGFR TKI samples available. None of the patients developed pneumonitis in this series, but given the potential risk of pneumonitis with osimertinib and CRT [16,27,28], the safety of this sequential approach requires further evaluation.

Conclusion

In summary, induction EGFR TKI before concurrent CRT achieved promising recurrence-free survival and was well tolerated in this series of patients with unresectable stage III *EGFR*-mutated NSCLC. In clinical practice, this strategy could be considered for patients with large tumors or extensive locally advanced disease, though when repeat assessment shows a response, it creates another decision point of whether to pursue CRT or maintain the EGFR TKI. Prospective studies are needed to define the role of induction EGFR TKIs in this setting, assess whether ctDNA analysis can be leveraged to help guide clinical decisions, and determine whether maintenance EGFR TKI enhances outcomes.

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CRediT authorship contribution statement

Jacqueline V. Aredo: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Heather A. Wakelee:** Resources, Writing – review & editing. **Angela Bik-Yu Hui:** Investigation, Writing – review & editing. **Sukhmani K. Padda:** Resources, Writing – review & editing. **Nitin D. Joshi:** Resources, Writing – review & editing. **H. Henry Guo:** Investigation, Writing – review & editing. **Aadel Chaudhuri:** Investigation, Writing – review & editing. **Maximilian Diehn:** Resources, Investigation, Writing – review & editing. **Billy W. Loo:** Resources, Writing – review & editing. **Joel W. Neal:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision.

Declaration of Competing Interest

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