REVIEW ARTICLE

Emerging Role of Targeted Therapies Combined With Radiotherapy in Inoperable Stages I to III NSCLC: A Review From the IASLC ART Subcommittee

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ABSTRACT

Precision oncology has transformed the management of NSCLC by tailoring treatment to the specific genetic alterations driving oncogenesis. Targeted therapies, such as tyrosine kinase inhibitors, have been found to dramatically improve survival in patients with advanced-stage NSCLC. However, treatment options remain limited for patients with early or locally advanced stage (I–III) NSCLC harboring driver mutations, when the disease is not resectable, or the patient is unsuitable for surgery due to poor fitness or comorbidities. There is growing interest in combining targeted therapies with radiotherapy to optimize treatment outcomes for this patient group. Notably, a progression-free survival benefit has recently been reported with the third-generation tyrosine kinase inhibitor osimertinib in patients with inoperable, EGFR-mutated, stage III NSCLC after chemoradiotherapy. A narrative review of the literature was performed using PubMed, OVID (EMBASE), and ClinicalTrials.gov to identify studies evaluating the combination of targeted therapies and radiotherapy in inoperable stages I to III NSCLC. This review provides a comprehensive overview of the incidence of actionable driver alterations and emerging clinical evidence on combining targeted therapies with thoracic radiotherapy in patients with inoperable stages I to III NSCLC. The toxicity profile of combination treatments, optimal sequencing strategies, ongoing clinical trials, and future perspectives in this field are highlighted. In summary, a clear biological rationale supports the synergistic effects of combining targeted therapies with radiotherapy in the neoadjuvant, concurrent, and adjuvant settings. Advanced clinical trial methodologies may facilitate further research in this area, particularly for rare genetic alterations, to improve outcomes for these patients.

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Background to Oncogenic Driver Mutations in NSCLC

The discovery of targetable oncogenes has significantly advanced the treatment of NSCLC, particularly adenocarcinoma, where driver mutations are present in 30% to 35% of cases.[1] Key mutations include *EGFR*, *ALK*, *KRAS*, *ROS1*, *NTRK*, *MET*, *RET*, *BRAF*, *NRAS*, *ERBB2*, and *PIK3CA*, which can now be detected more efficiently using next-generation sequencing (NGS).[2]

Although lung cancer is often diagnosed at an advanced stage (IV) with metastatic spread, targeted therapies, such as tyrosine kinase inhibitors (TKIs), have improved response rates, progression-free survival (PFS), and overall survival (OS) in stage IV NSCLC.[3–5] This success has raised questions about extending targeted treatments to earlier stage disease. Advances in screening are enabling earlier diagnoses,[6] and molecular testing is becoming increasingly relevant in stages I to III NSCLC due to emerging adjuvant and neoadjuvant treatment options.[7]

Currently, molecular testing in early stage NSCLC is primarily focused on EGFR mutations, such as exon 19 deletion and L858R substitution.[8] The ADAURA trial established osimertinib as adjuvant therapy for resectable EGFR-mutated NSCLC,[9] whereas the ALINA trial demonstrated improved disease-free survival (DFS) with adjuvant alectinib for ALK-positive patients.[10] However, many patients with stages I to III have inoperable disease. Recently, the LAURA trial suggests a PFS benefit with third-generation TKI osimertinib after chemoradiotherapy (CRT) in stage III unresectable EGFR-mutated NSCLC.[11]

Guidelines are evolving, with the National Comprehensive Cancer Network now recommending osimertinib post-CRT for inoperable stage III EGFR-mutated NSCLC.[12] Meanwhile, the role of immunotherapy (IO) in oncogene-driven NSCLC remains uncertain. Large trials excluded EGFR/ALK-positive patients,[13,14] as they derive limited benefit from IO, particularly in never-smokers.[15,16] Expanding molecular testing to include a broader range of driver mutations is crucial for optimizing treatment strategies in earlier stage disease.

Current Standard-of-Care Treatment for Inoperable, Stages I to III NSCLC

It is estimated that approximately 45% of patients have stages I to III disease at diagnosis.[17–19] The current standard-of-care therapy for patients with inoperable, stages I to II NSCLC is stereotactic ablative radiotherapy. In patients with inoperable, stages II to III disease, combined modality treatment, including radiotherapy, chemotherapy, and immunotherapy, is recommended.[20] However, the 5-year survival for patients with inoperable, stage III disease who undergo definitive CRT plus consolidation immunotherapy is 43%.[21]

Radiotherapy plays an essential role in the management of patients with stages I to III NSCLC. Nevertheless, local and distant failures are common. Targeted therapies are highly selective for the genetic alteration of interest. They have a different and generally more tolerable side effect profile compared with chemotherapy. The use of targeted agents in combination with radiotherapy in inoperable, stages I to III disease is an area of emerging interest.

Methods

This is a narrative review of the literature. OVID (EMBASE 1994–2024), PubMed (1950–2024), and ClinicalTrials.gov were searched with the terms "phase I-III trials, case-series, cohort studies, meta-analysis and reviews" using keywords "lung cancer, non-small cell lung cancer, radiotherapy, radiation therapy, driver mutation, (EGFR, ALK, ROS1, etc.) gene mutation, oncogene, targeted therapy, early stage and stage I-III, inoperable, unresectable." Papers published in English were reviewed. The list of references was created based on significance and relevance to this review. Conference abstracts with high relevance to this review topic were included.

For the purpose of this paper, the term inoperable disease refers to patients who cannot have surgery due to one or more of the following reasons:

- Disease-related factors: Tumors or mediastinal lymph node involvement deemed unresectable by a thoracic surgeon (e.g., T4 tumors, bulky N2 or N3).
- Technical factors: Tumors located in close proximity to critical structures, whereby surgical intervention carries excessive risk of surgical morbidity or mortality.
- Patient-related factors: Patients deemed unsuitable candidates for surgical intervention due to poor fitness and/or significant co-morbidities.
- Informed patient decision: Patients who decline surgery after consultation with a thoracic surgeon.

Incidence and Prognosis of Driver Mutations in Stages I to III NSCLC

Large-scale sequencing projects have compared the incidence of oncogenic driver mutations in stages I to III and stage IV NSCLC. In studies directly comparing the incidence of actionable oncogenic driver mutations

between these stages, no significant differences were identified (Table 1). Nevertheless, a wide variation in incidence has been reported between studies in the literature. The disparity observed is likely due to the rare nature of particular mutations, geographical variation (e.g., due to differences in environmental exposures or genetic predispositions), type of pathology specimens, and the NGS techniques available. The ongoing LEADER trial (NCT04712877) is a screening trial to determine the proportion of patients whose tumors harbor an actionable oncogenic driver mutation. The trial screens patients with stages IA2 to III, resectable NSCLC and directs them to suitable targeted neoadjuvant phase II therapy trials, such as the NAUTIKA1 umbrella trial (NCT04302025).[31]

The Early-*EGFR* study enrolled 601 patients with resected stages IA to IIIB NSCLC from 14 countries across Asia, Latin America, the Middle East, and Africa, focusing exclusively on *EGFR* mutations and subtypes.[32] Among the cohort (52.7% female, 64.2% nonsmokers), *EGFR* mutations were present in 51.0%, with exon 19 deletions being the most common subtype (48.5%).

In the study by Stephan-Falkenau et al.[26] (Table 1), a genomic actionable alteration was identified in 37% (210/567) of I to III NSCLC cases. There was no significant difference between actionable mutations identified in those with stages I to III versus stage IV NSCLC when sex, age, smoking history, and histology were balanced between groups. In the TRACERx study, multiple tumor samples were obtained from treatment-naive patients with resectable disease and repeat biopsy samples were taken on disease progression to assess the evolution of genomic change. In 68.6% of patients, the dominant oncogenic driver mutation was shared between the primary tumor and subsequent metastases.[23]

The impact of smoking on the development of actionable driver mutations is recognized in stage IV disease. Lung cancers in smoking patients have a high incidence of KRAS mutations and low *EGFR* mutations.[33] In a study involving 219 patients with stages I to III NSCLC, *EGFR*, *MET*, and *RET* alterations were significantly increased in never-smokers compared with smokers.[34] Zhang et al.[24] analyzed the genetic profile in 225 early stage, never-smoking patients with NSCLC and found lower incidence of *KRAS* and *TP53* mutations and higher incidence of *EGFR* mutations. As smoking rates continue to decrease in many countries, the proportion of patients with NSCLC who have never smoked has increased among all lung cancer cases.[35,36] This condition, known as lung cancer in never smokers (LCINS), is thought to exhibit unique clinical and genetic characteristics.[24] Ambient air pollution has also been associated with the development of EGFR-mutated lung adenocarcinoma, in those with underlying genetic predisposition (preexisting EGFR mutations identified in healthy lung tissue).[36] There is still much to learn about these entities, particularly regarding their implications for actionable driver mutation-driven NSCLC.

Prognosis has been found to vary according to oncogenic driver mutation status.[37] Patients with metastatic disease and *EGFR* mutations exhibit significantly longer survival compared with those with wild-type *EGFR* or *KRAS* mutation.[38] The availability of targeted therapies undoubtedly improves prognosis where available compared with patients with wild-type genotype. However, it is believed that different driver mutations harbor distinct clinicopathologic characteristics, accompanied by unique co-passenger mutations, implying inherent differences in treatment response. There is a paucity of data regarding the impact of driver mutations within the context of CRT. One study evaluated outcomes after trimodality treatment or concurrent CRT in stages II to III NSCLC ($n = 250$).[39] Its results revealed that 60% had an actionable oncogenic driver mutation; 32% *KRAS*, 19% *EGFR*, and 9% *ALK* translocation.

OS was significantly longer for patients with an *EGFR* mutation or *ALK* translocation compared with those with *KRAS* mutations or wild type (55.8 mo versus not reached versus 28.0 mo versus 33.2 mo; $p = 0.02$). In the multivariable analysis, *ALK* translocation was associated with significantly longer OS (hazard ratio 0.32, confidence interval 0.12–0.87, $p = 0.03$). The authors attribute the prolonged survival outcomes to early genotyping of patients and the use of this information to select effective targeted salvage therapy at recurrence, where available.

Rationale for Targeted Therapy in Combination With Radiotherapy in Inoperable, Stages I to III NSCLC

Evidence to support the use of targeted therapy in combination with radiotherapy originates from the stage IV setting, where numerous studies have revealed a survival benefit.[40–43] Several biological mechanisms have been proposed supporting the hypothesis that the combination of TKIs with radiotherapy may exert a synergistic and additive anticancer effect. These principles are explained in subsequent texts. Consequently, there is a scientific rationale for incorporating targeted therapies at different stages of the disease pathway in combination with radiotherapy in those with inoperable, stages I to III disease harboring oncogenic driver mutations.

Neoadjuvant Administration of Targeted Therapy

To "down-stage" disease, targeted agents may be administered before definitive treatment with radiotherapy, to reduce the volume of disease. A smaller, more encompassable radiotherapy volume may lead to better

Table 1. Incidence of Actionable Driver Mutations in Stages I to III and Stage IV NSCLC

Study Name and Reference	Total Number of Patients	Number of Stages I to III	Number of Stage IV	KRAS (G12C) %	EGFR %	ALK %	BRAF (V600E) %	MET %	RET %	ROS1 %	NRTK %	Non-Actionable or No Mutation%	Ethnicity or Country	Pathology Specimen
TCGA PanCancer Atlas[22]	197	197	0	28.4	11.4	6.1	8.6	4.6	4.6	5.1	2.5	28.7	United States. Most patients European.	Most surgical specimens from 33 different cancer types including lung NSCLC (adenocarcinoma and squamous cell carcinoma).
TracerX[23]	254	254	0	34.7	15.1	2.9	7.3	4.9	0.8	2.0	6.5	27.1	United Kingdom. No information reported on ethnicity.	Most surgical specimens from patients with primary NSCLC (adenocarcinoma).
Sherlock-Lung study. Zhang et al.[24]	232	232	0	7.1	29.3	0.5	0.5	2.7	0.5	ND	0.5	58.9	United States. European 94.5% (n = 226), Asian 1.7% (n = 4), African 0.9% (n = 2).	Tumor tissue from primary NSCLC (adenocarcinoma).
Wang et al.[25]	1356	1356	0	8.0	63.1	5.2	0.3	ND	1.3	0.8	ND	17.9	East Asia (China).	Surgical specimens (adenocarcinoma).
Stephen-Falkenau et al.[26]	1217	567	650	40.4 (17.3)	12.7	1.2	5.7 (1.8)	2.3	0.7	0.2	ND	63.8	Germany. All samples from White patients.	Surgical specimens and biopsy samples. (78% of specimens were adenocarcinoma)
				40 (15.7)	12	2.2	5.1 (2.2)	2.6	0.5	0.6	ND	64.2		
	p value			**0.5**	**0.77**	**0.31**	**0.44**	**0.85**	**0.71**	**0.37**	**ND**	**ND**		
Terranto et al.[27]	1961	513	1448	30.9 (10.3)	13.6	4.8	3.5 (1.9)	5.2	3.4	0.3	ND	60.5	Italy. All samples from White patients.	Surgical specimens and biopsy samples. (Adenocarcinoma)
				26 (10.1)	13.8	5.7	3.6 (2.5)	6.7	3.3	0.4	ND	57.5		
	p value			**ND**	**0.92**	**0.47**	**ND**	**0.68**	**0.97**	**0.78**	**ND**	**ND**		
Memorial Sloan Kettering (MSK) IMPACT[28]	1357	798	559	32.7	28.3	3.6	5.9	4.9	2.6	2.8	1.9	17.3	United States. No information available on ethnicity.	Surgical specimens, biopsy and cytology samples. (Adenocarcinoma)
				25.8	29.0	4.5	5.7	4.1	2.8	1.8	2.5	15.6		

(continued)

Table 1. Continued

Study Name and Reference	Total Number of Patients	Number of Stages I to III	Number of Stage IV	KRAS (G12C) %	EGFR %	ALK %	BRAF (V600E) %	MET %	RET %	ROS1 %	NRTK %	Non-Actionable or No Mutation%	Ethnicity or Country	Pathology Specimen
	p value			ND	0.63	0.16	ND	0.91	0.67	1	0.75	ND		
McGuire et al.[29]	212	53	159	32.1 (15.1)	22.1	1.9	1.9	5.7	3.8	1.9	ND	47.6	Canada. No information reported on ethnicity.	Surgical specimens and biopsy samples from primary NSCLC (83% were adenocarcinoma).
				27 (10.7)	27	5	9.4	3.1	0	0.6	ND	44.2		
	p value			0.4	0.23	ND	ND	0.4	ND	ND	ND	ND		

Note: *p* values are included where the incidence of stages I to III versus stage IV has been directly compared. Data from TGCA PanCancer Atlas, TracerX, Zhang, and MSK IMPACT accessed through CBioPortal for Cancer Genomics website.[30]
ND, no data.

efficacy of radiotherapy and reduced treatment-related toxicity. Preoperative treatment is generally better tolerated compared with adjuvant therapy.[44] This approach also treats micrometastatic disease at an early stage. Several trials, albeit involving small numbers of patients, receiving targeted therapy before surgery to date have demonstrated that neoadjuvant targeted therapy in NSCLC is feasible with good response rates, as summarized in a review by Lee et al.[44] Further evidence is required in this setting.

Concurrent Administration of Targeted Therapy

The principle of "biological cooperation" suggests that the combination of targeted therapies and radiotherapy administered simultaneously increases the number of inhibited mechanisms of the cell survival pathway, which enhances overall tumor cell kill and improves treatment response.[45] For example, the suppression of the *EGFR* pathway by TKI therapy inhibits the downstream *PIK3/AKT* and *RAS/RAF/MEK/ERK* pathways, which suppresses DNA damage repair, increases apoptosis, and reduces cell proliferation. Through *EGFR* blockade, cells with accumulated DNA damage are therefore more susceptible to radiation-induced DNA damage.[46] Other mechanisms whereby the addition of a TKI to radiotherapy exerts its synergistic effect include increased number of inactivated cancer stem cells, enhanced signalling of gene pathways linked to radiosensitivity, such as *CXCL1* and Egr-1, down-regulation of DNA repair genes (e.g., *RAD51*), and increased reoxygenation.[47,48] Furthermore, there are notable cell cycle effects. Studies have revealed that the administration of a TKI with radiotherapy results in a decrease in the number of cells in the relatively radioresistant S phase. This leads to heightened radiosensitivity, underscoring the potential efficacy of combination therapy.[49,50] Preclinical data are available to support this concept, which demonstrated significantly reduced tumor volume in *EGFR* and *ALK*-positive xenograft models.[49,51,52]

There is a risk of increased toxicity when administering a TKI concurrently with thoracic radiotherapy due to the overlapping lung toxicities. A meta-analysis evaluating first-generation *EGFR* TKI and radiotherapy revealed that the highest risk of more than or equal to G3 pneumonitis occurred with concurrent treatment. The estimated risk was 4.9% (95% confidence interval 2.5%–8.1%) from 26 studies involving 765 patients.[53] This is addressed further in the Challenges of Combining Targeted Therapy With Radiotherapy in Inoperable, Stages I to III NSCLC section.

Adjuvant Administration of Targeted Therapy

"Spatial cooperation" is a term used to describe the use of radiotherapy to treat localized disease followed by

systemic therapy to treat any residual micrometastatic disease, without an interaction between the two modalities.[45] The aim of additional targeted therapy being added to radiotherapy is to eradicate any remaining cancer cells and prevent future disease relapse. Platinum-based adjuvant chemotherapy has been the longstanding standard-of-care treatment after resection in those patients at high risk of relapse and has demonstrated a survival benefit.[54] In patients with stages IB to IIIA, resectable *EGFR* mutation-positive disease, adjuvant osimertinib is the new standard of care. A number of trials have been conducted in this setting (Table 2) and are ongoing for patients with other driver mutations (Table 3).

Evidence for Targeted Therapy in Combination With Radiotherapy in Inoperable, Stages I to III NSCLC

In patients with inoperable, stages I to III driver mutation-positive NSCLC, there is limited evidence supporting the use of targeted agents in the context of radiotherapy. The existing evidence is summarized in Table 2.

Challenges of Combining Targeted Therapy With Radiotherapy in Inoperable, Stages I to III NSCLC

Several challenges have been identified in combining targeted agents with surgery, many of which are relevant to their use alongside radiotherapy. First, access to genetic analyses remains inconsistent, leading to delays in obtaining results. There is a global disparity in access to and reimbursement for molecular testing in early stage NSCLC. However, with targeted treatment options emerging for stages I to III disease, genomic profiling should become a priority before multidisciplinary team decision-making.[8,68] Tissue availability is another limitation, as small diagnostic samples may not allow for all necessary tests. Cytologic samples and liquid biopsies offer potential solutions but face technical and clinical challenges, including detecting circulating tumor DNA (ctDNA) in early disease and standardizing testing procedures.[69] Ongoing trials are incorporating ctDNA testing, which will be critical for expanding its clinical application.[67,70]

The optimal duration of TKI therapy remains another open question. The ADAURA trial revealed a decline in DFS after 3 years, suggesting longer treatment might be beneficial.[71] Other trials have limited TKI use to 2 years,[72–74] though the ICOMPARE phase II trial demonstrated superior DFS with 2 years versus 1 year of icotinib in resected EGFR-mutated NSCLC.[75] In contrast, osimertinib in the LAURA trial was administered until progression.[11] Although indefinite TKI therapy raises concerns about toxicity, extended adjuvant treatment is common in other cancers.[76] Longer treatment durations in the neoadjuvant setting may also be required to achieve the same pathologic response as chemotherapy. Future strategies may involve ctDNA-guided treatment duration to address minimal residual disease and relapse risk.

Combining targeted therapy with CRT presents additional toxicity concerns. A TKI radiotherapy overlap of more than 20 days increases the risk of more than or equal to G2 pneumonitis,[77] and rates of more than or equal to G3 pneumonitis have reached 20%—higher than with chemoradiotherapy.[78,79] A phase II study of gefitinib with thoracic radiotherapy reported G1 to 2 pneumonitis in 89% of patients but no G3 to 5 toxicity, though 30% discontinued TKI treatment.[80] Another concern is increased toxicity when TKI therapy follows progression on immunotherapy due to the long half-life of these agents.[81,82] Until recently, safety data were limited to small studies with different generations of EGFR TKIs. However, the LAURA trial found no increased pneumonitis rates with osimertinib after CRT compared with placebo, with only 13% of patients experiencing more than or equal to G3 adverse events.[11]

EGFR-mutated stage III NSCLC carries a high relapse risk compared with non–oncogene-driven disease.[37] The control arms of the LAURA (stages IIIA–C) and POLESTAR (stage III) trials revealed poor outcomes (median PFS: 5.9 mo and 3.8 mo, respectively).[61,83] Positron emission tomography-computed tomography was not mandatory in LAURA and was performed in only 55% of the osimertinib arm and 45% of the control arm, suggesting some patients may have had undetected micrometastatic disease. However, PFS benefit was observed with osimertinib regardless of positron emission tomography-computed tomography staging.[83] In contrast, the FLAURA trial in stage IV NSCLC reported a median PFS of 18.9 months with osimertinib versus 10.2 months with standard EGFR TKI therapy.[84] Patients in FLAURA were treatment naive, which may explain their improved responses, whereas those in LAURA and POLESTAR had undergone CRT, potentially selecting for more resistant clones. Whether chemotherapy is needed alongside adjuvant TKI therapy post-CRT remains uncertain.

Optimizing the sequencing of TKI therapy across neoadjuvant, concurrent, and adjuvant settings is essential. The ADAURA, ALINA, and LAURA trials demonstrated that second- or third-generation EGFR/ALK TKIs significantly reduced relapse risk, particularly in the brain.[10,11,71] ADAURA is the only trial to report an OS benefit with adjuvant osimertinib in resected EGFR-mutated NSCLC,[9] whereas earlier trials of first- and

Table 2. Phase II to III Trials and Retrospective Studies Evaluating Radiotherapy in Combination With Targeted Therapy in Inoperable, Stages I to III NSCLC

Trial Name or Authors	Number of Participants	Disease Stage	Study Design	Trial End Point	Results/Comments
Neo-adjuvant setting					
RTOG 1306[55]	59	IIIA-IIIB	Randomized phase II trial. 12 wk of induction TKI (erlotinib or crizotinib) before CRT vs. CRT alone.	Primary - PFS. Secondary - Grades 3 to 5 adverse events, OS.	EGFR and ALK. Closed early due to poor recruitment.
LOGIK 0902[56]	20	III	Nonrandomized phase II study. Induction TKI (gefitinib) before CRT.	Primary - 2-y OS.	Met primary end point - 2-y OS 90%. No grade 3 or higher radiation pneumonitis.
Peled et al.[57]	24	III	Nonrandomized phase II study. Induction TKI (osimertinib) for 12 wk before RT (or surgery).	Primary - ORR. Secondary - safety, GTV, PTV and lung V20% before vs. after osimertinib.	ORR of 95.2%, median DFS was not reached after 28.7 mo. Also highlighted a significant reduction in the size of the radiation field, including GTV, PTV, and V20% lung.
Concurrent setting					
CALGB 30106.[58]	63	III	Phase II nonrandomized study evaluating addition of TKI (gefitinib) to sequential or concurrent CRT. (Patients with either performance status 2 or >5% weight loss received RT with TKI (gefitinib) alone.	Primary - OS. Secondary - ORR, PFS.	Close early due to poor survival in good risk patients, whose survival was lower than the poor-risk group (13.4 mo in good risk, 19.0 mo in poor-risk group). Molecularly unselected population, only 29% of tumors harbored EGFR mutations. Toxicity not increased compared with retrospective controls.
Fu et al.[59]	29	II	Nonrandomized phase II study. RT concurrent with TKI (gefitinib).	Primary - ORR. Secondary - ORR, PFS, OS and safety.	ORR was 75% (21/28), 19.9% (5/28) stable disease, and 7.1% (2/28) had progression of disease. Median OS 26.0 mo, PFS 11.0 mo.
RECEL[55]	40	IIIA/B	Randomized phase II study. TKI (erlotinib) concurrent with RT and adjuvant for up to 2 y, until disease progression or unacceptable toxicity.	Primary - PFS. Secondary - ORR and safety.	A significantly prolonged PFS was reported with erlotinib (PFS 24.5 vs. 9.0 mo, $p = <0.001$). Pulmonary toxicity was not increased with concurrent administration of TKI and RT compared with historical controls or chemotherapy.
Adjuvant setting					
SWOG S0023[60]	243	III	Randomized phase III trial. All patients received CRT, then randomized to either by TKI (gefitinib) vs. placebo.	Primary - OS. Secondary - PFS, toxicity, response rates.	Closed early due to inferior survival in the experimental arm vs. control arm (23.0 mo vs. 35.0 mo, p value = 0.013). G5 events 2% (n = 2) in the TKI group vs. 0% for placebo. Patients were not selected based on EGFR mutation status.

(continued)

Table 2. Continued

Trial Name or Authors	Number of Participants	Disease Stage	Study Design	Trial End Point	Results/Comments
LAURA[11]	216	III	Randomized phase III trial. All patients received CRT before being randomized 2:1 to either TKI (osimertinib) vs. placebo.	Primary – PFS. Secondary – OS, CNS PFS, safety.	Met primary end point - Median PFS of 39.1 mo with osimertinib vs. 5.6 mo with placebo. HR for death or disease progression 0.16 (95% CI 0.10–0.24, $p < 0.001$). Incidence of new brain metastases was lower with osimertinib (8% vs. 29% with placebo). Further overall survival data are awaited. Most adverse events were G1 to G2 and did not lead to treatment discontinuation. The rate of G3 radiation pneumonitis was 2% in the osimertinib group compared with 0% in the placebo group.
POLESTAR[61]	147	III	Randomized, phase III trial. All patients received CRT before being randomized to receive TKI (aumolertinib) or placebo.	Primary – PFS. Secondary – OS, safety.	Significantly improved PFS (30.4 mo compared with 3.8 mo (HR 0.200, $p = <0.0001$), based on an interim analysis presented at WCLC 2024. However, the PFS of the control group is much worse than expected. Long-term follow-up data are awaited.
Retrospective studies in the adjuvant setting					
Nassar et al.[62]	136	III	Retrospective study. CRT followed by adjuvant durvalumab (n = 56), *EGFR* TKI (osimertinib) (n = 33), or observation (n = 47).	Primary – rwPFS.	Significantly prolonged PFS at 24.0 mo with adjuvant osimertinib (86%) vs. durvalumab (36%) or observation (27%) ($p < 0.001$). G3 treatment-related adverse events 2 (6.1%) with TKI and 10 (18%) in durvalumab arm. No difference in OS between 3 cohorts, possibly due to limited follow-up (46 mo).
Aredo et al.[63]	37	III	Retrospective study. CRT followed by adjuvant durvalumab (n = 13), *EGFR* TKI (n = 8), or observation (n = 16).	Primary – PFS. Secondary – OS.	Median PFS was significantly longer 26.1 mo in TKI group vs. 6.9 mo observation. HR for recurrence was 0.16 with adjuvant TKI therapy. No significant difference between durvalumab consolidation vs. CRT alone. Immune-related toxicity G3 or higher was observed in five patients, including 1 patient with G4 pneumonitis after initiation of TKI on progression to durvalumab.

(continued)

Table 2. Continued

Trial Name or Authors	Number of Participants	Disease Stage	Study Design	Trial End Point	Results/Comments
Wang et al.[64]	242	III	Retrospective study. CRT followed by adjuvant durvalumab, *EGFR* TKI, or observation	Primary – OS. Secondary – PFS.	Patients exhibiting a driver mutation - EGFR (58.5%), KRAS, and ALK. Significantly prolonged median OS in those who received a consolidation therapy (either immunotherapy [n = 55] or targeted therapy [n = 58]), compared with those who received no consolidation therapy (not reached vs. 24.37 mo, $p = 0.006$). Significant improvement in median OS reported in those receiving consolidation TKI vs. immunotherapy ($p = .009$). PFS significantly prolonged with TKI compared with immunotherapy (42.97 vs. 17.17 mo, $p = 0.029$). Patients with *EGFR* mutations had significantly longer median OS compared with those with wild-type tumors, and there was no difference in those with tumors harboring *KRAS* mutation.
Other oncogenic driver mutations					
No studies identified.					

CNS PFS: central nervous system progression-free survival; CRT, chemoradiotherapy; DFS, disease-free survival; GTV, gross tumor volume; HR, hazard ratio; PTV, planned target volume; ORR, overall response rate; OS, overall survival; RT, radiotherapy; rwPFS, real-world progression-free survival; TKI, tyrosine kinase inhibitor; V20%, total lung volume minus GTV exceeding 20 Gy.

Table 3. Ongoing Phase II to III Trials Combining Radiotherapy With Adjuvant Targeted Therapy

Trial Name	Phase	Randomized	Patient Population	Intervention	Oncogenic Driver	Agent and Maximum Duration of Treatment	End Point
Adjuvant therapy							
HORIZON-01 (NCT05170204)	I-III	Yes	Stage III, inoperable	CRT	*ALK* translocation or *ROS1* fusion	Alectinib, entrectinib. Up to 3 y.	Primary - PFS, Secondary - TTCD, QOL, safety, time to CNS progression, DMFS, ORR, DOR, OS.
BOUNCE (NCT05718297)	II	Yes	Stage III, inoperable	CRT	*ALK* translocation	Brigatinib Up to 3 y.	Primary - PFS Secondary - OS, CNS relapse-free survival
LIBRETTO-432 (NCT04819100)[65]	III	Yes	Stages IB-IIIA, inoperable	CRT or surgical resection	*RET* fusion	Selpercatinib Up to 3 y.	Primary - EFS. Secondary - OS, TTDR.
PACIFIC-4 substudy (NCT03833154)[66]	III	Yes	Stages I/II, inoperable	SBRT	*EGFR* mutation	Osimertinib Up to 3 y.	Primary - PFS, Secondary - safety, OS.
PLATINUM (NCT05338619)[67]	II	No	Stage III inoperable	CRT	*EGFR* mutation	Lazertinib Until disease progression or unacceptable toxicity.	Primary -PFS Secondary - OS, ORR, DOR, TTDM, safety.

CRT, chemoradiotherapy; CNS, central nervous system; DCR, disease control rate; DFS, disease free survival; DOR, duration of response; DMFS, distant metastasis-free survival; EFS, event-free survival; MPR, major pathologic response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pCR, pathologic complete response; SBRT, stereotactic body radiotherapy; TTCD, time to confirmed deterioration; TTDM, time to death or distant metastases; TTDR, time to distant recurrence; TTP, time to progression.

second-generation EGFR TKIs failed to reveal OS benefits.[72,73,85,86] However, subgroup analyses suggest meaningful DFS improvements.[55,58,60,63,87,88]

The optimal use of TKIs at disease relapse remains an area of investigation. Resistance mechanisms to osimertinib, including MET amplification and C797S mutations, have been identified in advanced NSCLC.[89] Understanding genomic evolution at recurrence will be key to guiding treatment sequencing, and drug development for second line and salvage therapy remains crucial.

Given the high incidence of brain metastases in patients with driver mutations, clinical trials in inoperable NSCLC must prioritize agents with strong central nervous system penetration.[90–93] ADAURA demonstrated a 76% reduction in brain recurrence risk with adjuvant osimertinib, whereas the third-generation pan-EGFR TKI furmonertinib demonstrated superior central nervous system efficacy than gefitinib.[94] In ALK-positive NSCLC, the ALINA trial reported a 78% reduction in brain relapse.[10]

Limitations of the Current Evidence

The existing evidence base on combining radiotherapy with targeted therapy in inoperable, stages I to III NSCLC is still emerging. The studies summarized in Table 2 are primarily small-scale phase II or retrospective analyses, with a focus on stage III disease. The phase III LAURA trial and unpublished phase III POLESTAR trial report a PFS benefit only, with mature long-term OS data awaited.

Of the presented prospective trials, only two (CALGB 30106 and RTOG 1306) include processes to ensure radiotherapy quality assurance. There is a significant gap in evidence for inoperable early stage (I–II) disease, and no studies have been identified involving patients with other rare mutations, such as *ALK*, *KRAS*, or *BRAF*. Given these limitations, the authors emphasize caution in interpreting the strength and adequacy of the existing data. Ongoing trials are addressing these gaps, as highlighted in Table 3.

Ongoing Trials

The ongoing trials are discussed in Table 3.

Conclusion and Future Perspectives

Combining targeted therapy with radiotherapy in patients with driver mutation-positive, inoperable stages I to III NSCLC reveals promise as a therapeutic strategy. However, given the current limitations in the evidence base, there are insufficient data to supports its widespread implementation in clinical practice at this time. As testing for driver mutations in stages I to III disease is becoming standard practice, additional evidence will become available regarding the clinical relevance of

driver mutations in patients with inoperable, stages I to III NSCLC. Further trials are needed to ensure that key issues such as efficacy (including intracranial control), toxicity, sequencing, and treatment duration are robustly evaluated. Further research is imperative into the less common driver mutations, for which treatment options are currently lacking. As conducting multiple clinical trials targeting rare alterations will be challenging, platform or umbrella studies evaluating distinct targeted therapies for rare mutations are warranted. The previously mentioned NAUTIKA1 screening umbrella design trial and the CONCORDE phase I platform design trial, which evaluates DNA damage repair inhibitors in combination with radiotherapy, are innovative and effective trials designed to test multiple agents simultaneously.[31,95] It is important to consider pragmatic trial designs to optimize trial infrastructure, enhance inclusivity, and comprehensively evaluate the novel use of these agents in combination with RT in molecularly selected patient populations. This research is crucial to drive drug development forward, ultimately enabling patients to access precision medicine and evidence-based treatments in a timely manner.

CRediT Authorship Contribution Statement

Sarah Bowen Jones: Conceptualization, Methodology, Writing - original draft, Writing - review and editing.

Clara Chan: Conceptualization, Methodology, Writing - review and editing.

Andrea R. Filippi: Conceptualization, Methodology, Writing - original draft, Writing - review and editing.

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