TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2025;40(Supp 1):7–21
doi: 10.5505/tjo.2025.2

REVIEW

New Targets, New Agents, and Radiotherapy in Non-small Cell Lung Cancer

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SUMMARY

The rapid integration of new molecularly targeted therapies and immune checkpoint inhibitors has fundamentally transformed the management of non–small cell lung cancer (NSCLC) across all stages. In early-stage disease, biomarker-driven strategies now enable adjuvant osimertinib for EGFR-mutated tumors and adjuvant alectinib for ALK-rearranged tumors, while neoadjuvant and perioperative chemo-immunotherapy have improved pathologic response and survival outcomes in driver-negative disease. In unresectable stage III NSCLC, concurrent chemoradiotherapy (cCRT) followed by consolidation durvalumab remains the standard for driver-negative patients. By contrast, in EGFR-mutated tumors, consolidation osimertinib after chemoradiotherapy (CRT)—supported by the LAURA trial—has produced a marked improvement in progression-free survival, redefining care for this molecular subset. For ALK-rearranged unresectable tumors, the role of targeted consolidation is under active investigation, with retrospective series favoring ALK tyrosine kinase inhibitor strategies over immunotherapy consolidation. In oligoprogression—particularly on TKIs—stereotactic body radiotherapy (SBRT) can eradicate resistant clones, prolong systemic benefit, and allow continuation of the same systemic agent. In patients with brain metastases harboring targetable alterations, the high intracranial activity of contemporary EGFR and ALK TKIs supports deferred radiotherapy in carefully selected patients. Despite these advances, critical questions persist regarding optimal sequencing, timing, treatment duration (including the appropriate length of adjuvant targeted therapy), and the safest, most effective integration of RT with novel agents. This review synthesizes current evidence and evolving strategies for combining new systemic agents and RT in NSCLC, offering a pragmatic, stage- and biology-specific framework to guide multidisciplinary decision-making.

Keywords: Immune checkpoint inhibitors; lung cancer; radiotherapy; targeted therapies.

INTRODUCTION

The rapid integration of molecularly targeted therapies and novel systemic agents has fundamentally transformed the management of lung cancer. In addition to new molecular targets and innovative agents, clinical practice is now defined by a growing diversity of patient scenarios, requiring individualized therapeutic strategies. This manuscript outlines how these agents are used in lung cancer and how they integrate with radiotherapy (RT), illustrated through key clinical scenarios.

RESECTABLE STAGE IB–IIIA

Resectable Stage IB–IIIA EGFR-mutated NSCLC

EGFR-Mutated NSCLC: EGFR mutations are detected in approximately 21% of patients with NSCLC. Exon 19 deletions and L858R mutations account for ~50% of these alterations. These tumors are characterized by a high propensity for distant and brain metastases, emphasizing the need for systemic strategies that provide effective systemic micrometastatic disease control and central nervous system (CNS) penetration. First-

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Turk J Oncol 2025;40(Supp 1):7–21
doi: 10.5505/tjo.2025.2

Table 1 Evolution of EGFR-TKIs and their clinical outcomes

Generation	Years	Agents	Mechanism	Median PFS (mPFS)
1st generation	2004–2013	Gefitinib, Erlotinib	Reversible EGFR inhibition	9–10 months
2nd generation	2013–2015	Afatinib, Dacomitinib	Irreversible EGFR inhibition	11–14 months
3rd generation	2015–present	Osimertinib, Lazertinib	Irreversible, effective against T790M mutation	19 months

EGFR-TKIs: EGFR tyrosine kinase inhibitors; PFS: Progression free survival

generation EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, represented an important initial advance; however, third-generation agents like osimertinib now offer superior intracranial activity and durable disease control and potently and selectively inhibits both EGFR-TKI sensitising and EGFR T790M resistance mutations. Osimertinib achieves greater intracranial concentrations compared to first- and second-generation TKIs and has been demonstrated to have significant intracranial activity against brain metastases at the standard dose of 80 mg daily, and even against leptomeningeal carcinomatosis at 80 to 160 mg daily[1,2] (Table 1).

Management Approach in Resectable Stage IB–IIIA EGFR-mutated NSCLC

The optimal management approach for patients with resectable stage IB–IIIA EGFR-mutated NSCLC has been informed by the results of the ADAURA trial. Adjuvant osimertinib administered for three years following complete resection of stage I–IIIA EGFR-mutated NSCLC has been associated with early and sustained improvements in disease-free survival (median DFS [95% CI], 65.8 months [54.4–NC] vs 21.9 months [16.6–27.5]). Adjuvant chemotherapy was optional in both the study and the control arm. Treatment with preoperative, postoperative, or planned radiation therapy was not allowed. The DFS benefit with osimertinib emerged early and was consistent across all predefined subgroups, including all disease stages. Notably, a clinically meaningful improvement in CNS disease-free survival was observed, underscoring the drug's robust intracranial efficacy. At 24 months, 98% of the patients who received osimertinib and 85% of those who received placebo were alive without CNS disease (overall hazard ratio (HR) for CNS disease recurrence or death, 0.18; 95% CI, 0.10 to 0.33). Thus, adjuvant osimertinib reduced the risk of CNS recurrence among patients with resected EGFR mutation– positive NSCLC.[3] However, discontinuation of therapy at three years is associated with a sharp increase in intracranial relapse, underscoring the need for ongoing surveillance and raising questions regarding the optimal duration of therapy.

Resectable Stage IB–IIIA ALK-rearranged NSCLC

ALK-Rearranged NSCLC: ALK rearrangements are identified in approximately 3–7% of NSCLC cases, typically in younger patients and in those with no history of smoking. Pleural involvement or pleural effusion may be present, and these patients exhibit a predisposition to thrombosis and a high lifetime risk of brain metastases (~70%). Typically diagnosed at a younger age, these patients often experience disease recurrence and carry a higher risk of developing brain metastases compared with those with other types of NSCLC.

First-generation therapy includes crizotinib. Second-generation agents comprise ceritinib, alectinib, ensartinib, and brigatinib, while lorlatinib represents the third-generation ALK TKI. The successive generations of ALK TKIs have demonstrated an increasing potential to overcome ALK resistance, leading to incremental improvements in systemic efficacy. Third-generation lorlatinib additionally achieves the highest CNS penetration, enhancing intracranial efficacy.

Management Approach in Resectable Stage IB–IIIA ALK-rearranged NSCLC

For stage IB–III NSCLC with ALK rearrangements, upfront surgery followed by 2 years of adjuvant alectinib is the preferred approach, based on data from the ALINA trial. In the adjuvant setting, two years of alectinib compared with platinum-based CT following curative resection of stage I–IIIA ALK- rearranged NSCLC (none of the patients received preoperative or postoperative RT) has demonstrated marked prolongation of disease-free survival 76% reduction in the risk of disease recurrence or death over platinum double chemotherapy (HR=0.24, 95% CI: 0.13–0.43, p<0.0001), including durable intracranial control (HR=0.22; 95% CI: 0.08–0.58), which is of particular relevance to patients with ALK-rear-

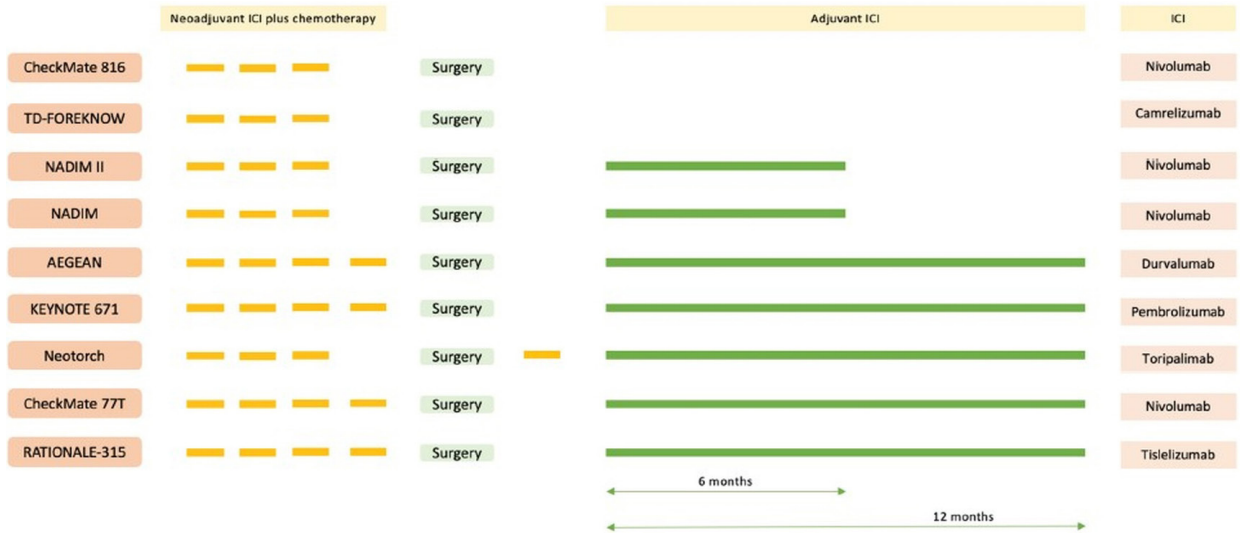

Fig. 1. Schema of phase II/III trials investigating neoadjuvant immune checkpoint inhibitors in resectable NSCLC.
NSCLC: Non–small cell lung cancer.

rangements given the predilection for brain metastases – estimated at up to 70% lifetime risk.[4] These findings have established alectinib as the standard of care in this setting and highlight the importance of early molecular testing to guide postoperative decision-making.

Molecular Testing in Early-stage NSCLC

The biomarker-driven approach that transformed the metastatic landscape has now extended to early-stage disease. Since the patients with common sensitizing EGFR mutations or ALK-rearrangements may be candidates for adjuvant osimertinib or alectinib respectively and as patients with EGFR mutations and ALK-rearrangements were generally excluded from most of the peri-operative immunotherapy (IO) plus chemotherapy trials (because the response rate to IO and survival benefits in patients with an oncogene driven NSCLC, are low), non-squamous NSCLC tumours should be tested for these two oncogenic alterations.[5] Accordingly, comprehensive testing for EGFR mutations, ALK rearrangements, and PD-L1 expression is now recommended for all patients with stage IB–IIIA disease to inform both adjuvant and peri-operative treatment strategies. This shift reflects the increasingly recognized heterogeneity of early-stage NSCLC and the need to tailor systemic therapy according to tumor biology.

In addition, PD-L1 expression serves as a predictive biomarker of response in peri-operative settings, with higher levels correlating with increased rates of pathologic response; In cases with PD-L1 scores >50%, the pCR rate is higher compared to those with PD-L1 TPS of 1–49% or <1%.[6,7]

RESECTABLE STAGE IB–IIIA NSCLC WITHOUT ACTIONABLE MUTATIONS

Management approach in patients with resectable stage IB–IIIA NSCLC, EGFR-negative, ALK-negative, and PD-L1 expression >1%

Integration of IO

The most commonly used IO agents in lung cancer and their mechanisms of action are summarized as follows: Ipilimumab is a human cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor that facilitates CD80/CD86–CD28 binding and promotes T-cell activation. Pembrolizumab, nivolumab, durvalumab, and atezolizumab are anti–PD-(L)1 antibodies that block the interaction between PD-1 and PD-L1, thereby restoring anti-tumor T-cell activity.

What is the Preferred Approach? Adjuvant? Neoadjuvant? Perioperative?

The addition of immune checkpoint inhibitors to the treatment paradigm has expanded therapeutic options for driver-negative tumors. IO can be delivered as adjuvant therapy following surgery, as neoadjuvant chemo-IO, or as a peri-operative approach combining preoperative Chemo-IO and postoperative IO administration.

Turk J Oncol 2025;40(Supp 1):7–21
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Table 2 Pathologic response outcomes (mPR and pCR) in neoadjuvant and perioperative immunotherapy trials

Study	Stage	Treatment	Down stage	pCR (%)	MPR (%)
CheckMate 816 Faz III [9]	IB–IIIA	Neo Nivo CT vs neo CT	30.7% vs. 23.5% (all stages)	24.0	36.9
NADIM II Faz II [11]	IIIA-IIIb	Neo Nivo + CT + Adjuvan Nivo	Nodal 72% vs. 40%	37.0	52.0
NADIM Faz II [12]	IIIA	Neo Nivo + CT + Adjuvan Nivo vs Neo CT	90% patological	56.5	73.9
AEGEAN Faz III [13]	IIA–IIIB	Neo Durva + CT + Adjuvan Durva vs Neo CT	–	17.2	33.3
CheckMate 77T Faz III [14]	IIA–IIIB	Neo Nivo + CT + Adjuvan Nivo	–	25.3	35.4
KEYNOTE 671 Faz III [15]	IIA–IIIB	Neo Pembro + CT + Adjuvan Pembro	–	18.1	30.2
NEOTORCH Faz III [16]	IIA–IIIB	Neo Toripalimab + CT + Adjuvan toripalimab	–	24.8	48.5

MPR: Major pathologic response; pCR: Pathological complete response; CT: Chemotherapy

There has been a rapid accumulation of evidence for neoadjuvant and perioperative approaches.[8] (Fig. 1).

The IMpower010 trial showed that adjuvant atezolizumab improved DFS after platinum-based chemotherapy in resected stage II–IIIA NSCLC, with the greatest benefit observed in patients with PD-L1 expression ≥50% (HR≈0.43), where the median DFS was not reached with atezolizumab vs 35.3 months with best supportive care.[9]

The CheckMate 816 trial with 5 years of follow-up demonstrated that adding neoadjuvant nivolumab to platinum-doublet chemotherapy in patients with resectable stage IB–IIIA NSCLC, demonstrated a statistically significant OS benefit compared with chemotherapy alone (median [95% CI], not reached [NR] versus 73.7 months [47.3–NR]; HR [95% CI], 0.72 [0.523–0.998]; p=0.0479). Patients who achieved a complete pathologic response with nivolumab plus chemotherapy experienced "sustained OS improvement" compared to those who did not (HR [95% CI], 0.11 [0.04–0.36]), with 5-year OS rates of 95% versus 56%. In addition, neoadjuvant with 5 years of follow-up nivolumab plus chemotherapy continued to improve EFS compared with chemotherapy, showing a median EFS of 59.6 months (95% CI, 31.6–NR) compared with 21.1 months (95% CI, 16.5–36.8; HR [95% CI], 0.68 [0.51–0.91]).[10]

Although no definitive evidence currently favors one approach over the others,[11] peri-operative regimens have demonstrated high levels of efficacy, with pathologic complete response rates approaching 30% and major pathologic response rates up to 50% These unprecedented response rates have introduced new concepts—such as major pathologic response—that are now being incorporated into clinical endpoints for early-stage disease[10,12–17] (Table 2).

For patients with resectable stage III NSCLC without actionable genomic alterations, these strategies have redefined the standard of care, often superseding surgery-first approaches irrespective of PD-L1 status. In earlier stages, particularly in tumors with high PD-L1 expression, peri-operative or neoadjuvant chemo-IO is increasingly being considered as a viable alternative to upfront surgery.[5,7]

Why Chemo-immunotherapy Combination?

In patients with PD-L1 expression of 1–49% or <1%, immune checkpoint inhibitors (ICIs) confer a survival benefit when combined with chemotherapy. This advantage is likely due to chemotherapy facilitating immune system priming and thereby augmenting anti-tumor immune responses.[18]

Assuming Equal Accessibility, is There a Preferred PD-(L)1 Inhibitor in the Peri-operative Setting?

Several phase III studies involving the use of ICI in the peri-operative setting for resectable NSCLC have demonstrated relatively consistent benefits with different PD-(L)1 inhibitors. Currently, there is no head-to-head evidence to confirm which ICI is superior.[11]

What is the Preferred Time Interval between Completion of Neoadjuvant IO Plus Chemotherapy and Surgical Resection?

It is 4–6 weeks.[5]

With neoadjuvant and perioperative approaches, the interval to surgery does not appear to be prolonged. On the contrary, the adoption of minimally invasive surgical techniques has increased, operative times have decreased, the frequency of pneumonectomy has declined, and R0 resection rates have improved.[19]

Table 3 Proportion of patients who failed to proceed to surgery in studies evaluating perioperative approaches

	NADIM II [8]	CheckMate 816 [7]	KEYNOTE 671 [12]	NEOTORCH [13]	AEGEAN [10]	CHECKMATE 77 T [11]
Surgery cancelled	7%	17%	18%	18%	19%	20%

What are the Definitions of pCR, Non-complete Response, and Major Pathological Response?

A pathological complete response was defined as 0% residual viable tumour cells in the resected specimen and sampled lymph nodes. A non-complete response was defined as presence of any residual viable tumour cells in the resectedprimary specimen and sampled lymph node after neoadj therapys, including major pathological responses (ie, ≤10% residual viable tumour cells) and incomplete pathological responses (ie, >10% residual viable tumour cells).[12]

The Role of RT in the Era of Peri-operative and Multimodal Approaches

The precise role of RT in the evolving landscape of perioperative treatment strategies remains an area of active debate. Current NA and peri-operative chemo-IO trials were not designed to systematically evaluate local-regional control or the potential impact of adjuvant RT leaving significant knowledge gaps. In fact, only one trial (Checkmate 816) has reported on local-regional recurrence, with an incidence of approximately 19%, a figure that is not negligible and underscores the ongoing importance of RT in comprehensive treatment planning.[10] It should be kept in mind that the follow-up durations of these studies are not yet mature enough to adequately assess local recurrences, and detailed information regarding RT is not available. Consequently, as new systemic strategies emerge, RT remains a critical component of the multidisciplinary discussion.

Similarly, for patients initially planned for a perioperative strategy who subsequently become ineligible for surgery (approximately 20% of cases)—whether due to disease progression (approximately 3–7% of cases), decline in performance status, treatment-related toxicity, or impaired pulmonary function—a multidisciplinary reassessment should be undertaken. In such cases, radical CRT should be pursued, provided no distant metastases are present and the disease can still be encompassed within a reasonable RT field.[7] Proportion of patients who failed to proceed to surgery in studies evaluating perioperative approaches is summarized in Table 3. Careful patient selection is vital. Unfortunately, there is not enough evidence that may help in choosing patients with resectable NSCLC for NA IO-chemo plus surgery +/- IO vs. immediate surgery plus adjuvant chemotherapy and ICI.[11]

UNRESECTABLE STAGE III NSCLC

Unresectable Stage III NSCLC without Actionable Mutations

In a patient with oncological and technically unresectable adenocarcinoma (ALK-negative, EGFR-negative, PD-L1 >1%) or squamous cell carcinoma (PD-L1 >1%), the optimal approach is concurrent platinum-based CRT followed, in the absence of disease progression, by maintenance durvalumab at a dose of 10 mg/kg every two weeks for one year. Durvalumab consolidation was associated with both favorable progression free survival (PFS) and overall survival (OS) with (HR 0.55; 95% confidence interval [CI], 0.45–0.68) and 0.72 (0.59–0.89), respectively. Five-year PFS and OS rates improved from 19% to 33% and 33% to 43%, median survival approaching 47 months with a manageable safety profile and did not detrimentally affect patient-reported outcomes compared with placebo. These unprecedented outcomes have redefined the standard of care in the management of locally advanced NSCLC.[20]

All-grade, grade 3–4, and grade 5 pneumonitis attributed to either radiation or IO occurred in 33.9%, 3.4%, and 1.5% of patients, respectively.[20]

Several important considerations should be kept in mind when interpreting this study. First, the criteria used to define inoperability, the extent of lymph node involvement, tumor volume, and specific RT parameters were not reported. Furthermore, patient enrollment was not restricted by oncogenic driver gene mutation status or PD-L1 expression and stratification was limited to age, sex, and smoking status, without incorporating TNM stage as a stratification factor, despite approximately 40% of the cohort comprising stage IIIA disease. Further research is required to determine the optimum duration of durvalumab treatment following CRT. Use of a 12-month treatment duration in PACIFIC was an empirical decision made based on the regimen used in a phase I/ II first-in-human study of durvalumab.

Turk J Oncol 2025;40(Supp 1):7–21
doi: 10.5505/tjo.2025.2

Patients with unresolved grade 2 toxicities or grade 2 pneumonitis and/or radiation pneumonitis from prior CRT should be excluded from PACIFIC regimen. According to real-world data, about 30% of patients are unable to receive durvalumab after CRT, with disease progression and grade ≥2 radiation pneumonitis being the most common reasons.[21] Besides, in Pacific trial about 50% of patients were able to complete the full year of treatment, while 15% discontinued due to toxicity (mostly pneumonitis, radiation pneumonitis, and pneumonia) and 31% discontinued due to disease progression.[20]

In real-world settings, the proportion of patients eligible for and able to complete the PACIFIC regimen is quite limited. Retrospective series showed that only half of the patients with stage III NSCLC are treated with radical intent in daily practice, and of those receiving CRT, only 2/3 are treated with CCRT whereas 1/3 received sequential chemoradiotherapy (sCRT). Furthermore, not all the patients treated with CCRT are eligible for adjuvant durvalumab due to residual toxicity, impaired PS, disease progression and, a programmed death-ligand 1 (PD-L1) level <1%. For patients not cured with, or not eligible for adjuvant durvalumab, new treatments are urgently needed. Conversely, 20% of patients are already cured after CCRT and do not need adjuvant durvalumab; identifying those patients would avoid unnecessary durvalumab-related toxicities and societal costs.[22]

Following the PACIFIC trial, numerous studies have investigated the optimal timing, sequencing, and combinations of CRT and IO in locally advanced NSCLC. Here, we aim to summarize some of the most notable among these.

A key insight from PACIFIC is the importance of timing. Although the optimal timing for initiating-durvalumab after the completion of chemoradiation has not been identified, PFS and OS were better in the subgroup of patients administered durvalumab within 14 days after the last radiation to randomization (PFS: HR 0.39, OS: HR 0.42).[20] This synergy is biologically plausible, as radiation upregulates PD-L1 expression and enhances antigen presentation, while durvalumab reverses radiation-induced immune suppression, promoting a robust systemic anti-tumor response.[23] Therefore, patients should undergo early radiological response assessment immediately after the regression of CRT-related toxicities. There did not seem to be a clinically meaningful association between the incidence or severity of grade greater than or equal to 2 pneumonitis or RT-pneumonitis and whether patients were randomized within or beyond 14 days of completing CRT, suggesting that durvalumab initiation should not be delayed for the sole purpose of reducing the risk of pneumonitis.[20] Of note, selection bias in the PACIFIC trial should be considered. If patients after cCRT were in good condition without immediate severe AEs (eg. patients with smaller disease volumes and a lower lung RT dose may have recovered from CRT more rapidly) they could start consolidation durvalumab earlier, probably within 14 days. However, if researchers initiated durvalumab later, they could have a better chance to screen out patients who are predisposed to progression. Either possibility could have resulted in biases. Since the PACIFIC trial demonstrated a benefit when durvalumab was initiated within 14 days after completion of CRT, and the clinical necessity to prevent the risk of disease progression during CRT the PACIFIC-2 trial evaluated the use of durvalumab in combination with and following CRT. However, this combination did not demonstrate a statistically significant improvement in progression-free survival (PFS) and OS likely due to the immunosuppressive effects of high-volume thoracic irradiation during active IO.[22,24] Consequently, sequential durvalumab remains the standard of care.

Following the lack of benefit observed with concurrent durvalumab administration subsequent efforts have focused on combination strategies in the maintenance setting, leading to phase 2 COAST trial of durvalumab in combination with either monalizumab or oleclumab after cCRT. Results showed that both durvalumab plus monalizumab and durvalumab plus oleclumab improved objective responses compared with durvalumab alone. Safety with either combination was not significantly different from the durvalumab-alone arm.[25] Data from COAST warranted a further evaluation of the durvalumab-based combination in a phase 3 PACIFIC-9 clinical trial and is expected to be completed in 2026.

Given the frequent use of sCRT in real-world clinical practice, the question of whether durvalumab can be administered safely after sCRT, with the goal of improving outcomes for patients who receive CRT in this manner, is of considerable interest. PACIFIC-6was designed to evaluate the safety and tolerability of durvalumab after sCRT. In this setting, the safety profile of durvalumab was consistent with the profile observed in the PACIFIC trial, in which durvalumab was administered after platinum-based cCRT. Only five of 117 patients (4.3%) had grade 3 or 4 PRAEs within 6 months

of starting treatment, demonstrating that durvalumab was generally well tolerated after sCRT. Twelve-month OS was 84.1%, and median PFS was 10.9 months.[26] These results suggest that the survival outcomes of patients receiving durvalumab after sCRT may be comparable to those of patients treated with cCRT.

According to current evidence chemo-IO is considered the preferred neoadjuvant approach exclusively for patients with resectable stage III-N2 NSCLC and has not addressed whether unresectable tumours can be converted to resectable via neoadjuvant treatment. Surgical resectability should be determined at the time of initial diagnosis in a dedicated multidisciplinary tumor board. For patients with unresectable, driver-negative, PD-L1–positive tumors, the sequential PACIFIC regimen remains the optimal strategy. Attempts to substitute concurrent regimens in hopes of downstaging disease are not currently supported by evidence and may deprive patients of the survival benefit conferred by the standard PACIFIC approach.[22] Therefore, the role of neoadjuvant therapy in downstaging unresectable NSCLC to resectable disease remains exploratory and should not be routinely recommended in clinical practice.

Unresectable Stage III EGFR-mutated NSCLC

Management Approach in Unresectable Stage IIIB EGFR Mutation-positive NSCLC

The patients with EGFR-mutated unresectable stage III disease, consolidation durvalumab does not provide meaningful benefit.[27] Instead, consolidation osimertinib following CRT has demonstrated an unprecedented improvement in progression-free survival, with approximately a six-fold increase compared to placebo.[28] Although crossover limited the OS signal, this approach has become the new standard of care for this molecular subset.

The PACIFIC trial established the role of consolidation durvalumab after definitive cCRT for patients with unresectable stage III NSCLC. However, subgroup analysis from PACIFIC and real-world data suggested limited benefit from consolidation durvalumab among patients with EGFR or ALK mutations.[27] This is in keeping with observations in the metastatic setting where patients with EGFR or ALK mutations generally derive limited benefit from ICI monotherapy. The recently published LAURA trial to assess the efficacy and safety of Osimertinib following chemoradiation in patients with stage III unresectable EGFR-mutated NSCLC Patients were randomized to receive either Osimertinib until progression or placebo group after completing CRT. Recently, Lu et al.[28] reported the interim analysis of LAURA trial. In patients with unresectable stage III EGFR-mutated NSCLC, consolidation Osimertinib after CRT led to impressively prolonged PFS (39.1 months (95% CI, 31.5 to not calculable) with Osimertinib and 5.6 months (95% CI, 3.7 to 7.4) with placebo; the overall HR for disease progression or death was 0.16) marking a paradigm shift in the treatment of locally advanced EGFR-mutant NSCLC.[27] OS was not significantly improved at this interim analysis, because of crossover at progression on placebo, 81% of patients received Osimertinib. It appears that only a minority of patients in LAURA—probably fewer than 10%—have long term disease-free survival without Osimertinib. Therefore, indefinite treatment may also offer advantages in protecting against intracranial metastases, a common site of recurrence in the control arm which did undergo routine surveillance brain MRIs. However, it also raises concerns such as potential side effects and increased cost burden. While some patients will discontinue due to side effects or personal preference, we hope that eventually ultrasensitive methods of residual tumor detection, likely either circulating tumor DNA molecular residual disease testing, or more sensitive imaging, could identify those in whom it is safe to discontinue and proceed with observation alone, because they may actually be cured, or alternatively, identify early signs of progression to restart therapy in those who have chosen to discontinue. The biomarker-guided adaptive therapy warrants further exploration due to its potential to enable patients to benefit from "drug holidays".[29]

The subgroup analyses of CNS PFS and TTDM from LAURA further build on the efficacy of osimertinib by demonstrating reduced risk of both distant metastases and CNS progression in patients with unresectable stage III EGFR-mutant NSCLC who had not progressed during or following definitive CRT, consistent with the PFS benefit. Compared with placebo, osimertinib was associated with an 83% reduction in the risk of CNS progression or death (HR for CNS PFS 0.17; 95% CI 0.09–0.32; $p<0.001$), with a 79% reduction in the risk of distant metastases or death (HR for TTDM 0.21; 95% CI 0.11–0.38; $p<0.001$).[28]

Unresectable Stage III ALK-rearranged NSCLC

Likewise, for patients with advanced ALK-rearranged NSCLC typically have poor response to IO; the benefit of consolidation durvalumab in patients with un-

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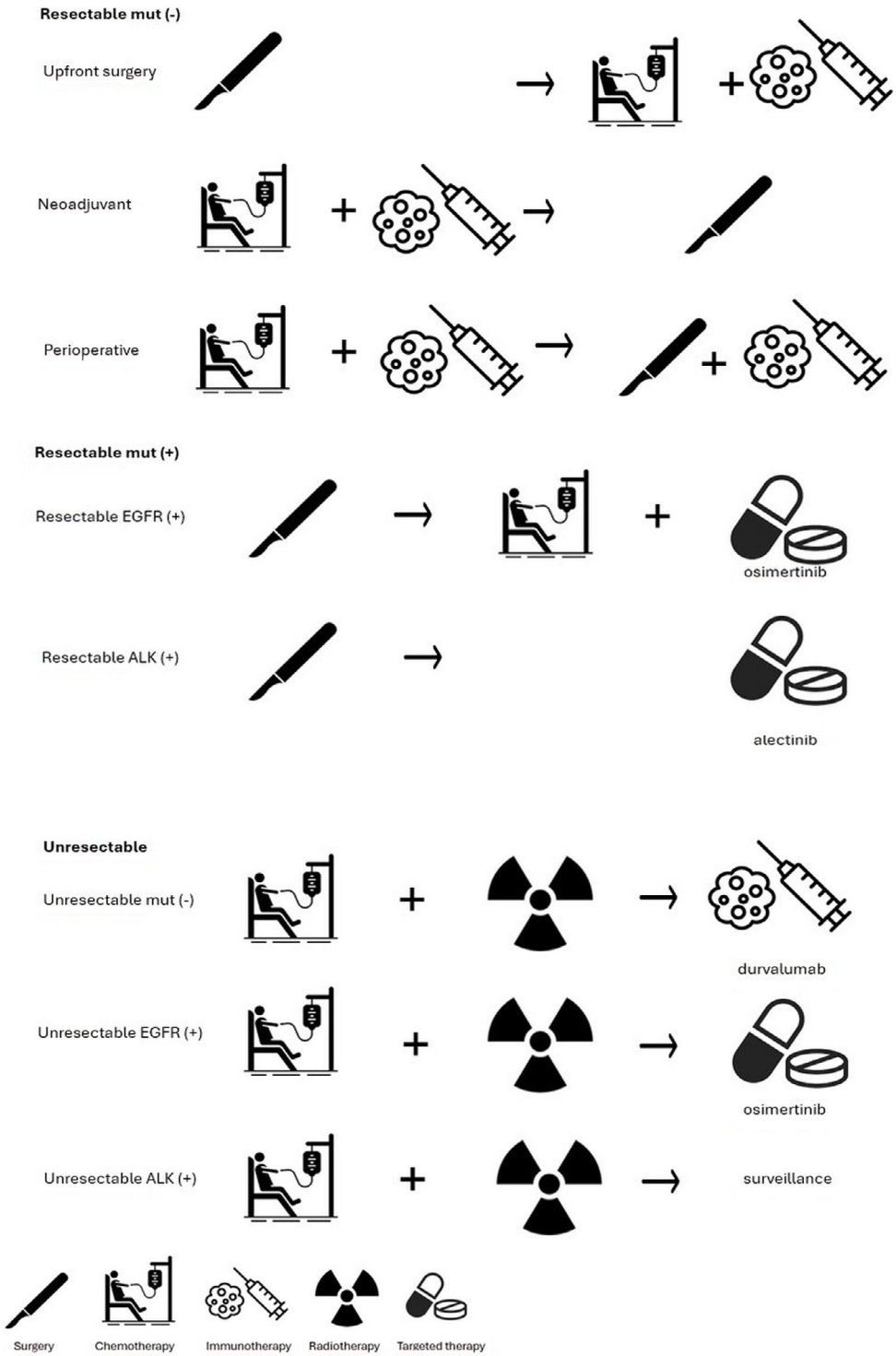

Fig. 2. The biology-specific treatment framework.

resectable stage III ALK- rearranged NSCLC remains unclear. Randomised data for patients with ALK-rearrangements is awaited. According to retrospective multicenter study of 17 institutions, patients with ALK- rearranged NSCLC experience significantly improved rwPFS when treated with consolidation ALK TKI therapy, surpassing outcomes found with either durvalumab or observation. We should not give con-

Table 4 Metastasis-directed radiotherapy in oligoprogressive disease: Summary of phase II randomized trials

Trial	CURB [23]	STOP [26]	HALT [27]	SUPPRESS-NSCLC [28]
KHDAK patient number	59/99	40/127	110	66
Disease	Oligoprogresive	Oligoprogresive	Oligoprogresive	Oligoprogresive
Number of met. lesion	≤5	≤5	≤3	≤5
RT dose	27–30 Gy/3 fr 30–50 Gy/5 fr	35 Gy / 5 fx 50Gy / 5 fr 48 Gy / 4 fr	SBRT	SBRT
PFS (control vs RT)	PFS: 2.2→10 month HR:0.41 OS: immature	PFS:NS OS :NS		
PFS difference	+7.8 month	–		
Toxicity	G3 15% vs 10%	3.4%		

NSCLC: Non-small cell lung cancer; RT: Radiotheraphy; SBRT: Stereotactic body radiotherapy; PFS: Progression free survival; OS: Overall survival; NS: Non significant

solidation durvalumab to these patients in view of the limited efficacy and concerns of overlapping toxicity when ICI are given prior to ALK TKI.[30]

Summary of the Current Treatment Algorithm

These data collectively inform a stage- and biology-specific treatment framework (Fig. 2):

- Resectable, driver-negative disease: Upfront surgery followed by adjuvant or neoadjuvant or perioperative chemo-IO.
- Resectable, driver-positive disease: Upfront surgery followed by targeted adjuvant therapy according to the identified driver mutation.
- Unresectable, driver-negative disease: cCRT followed by consolidation durvalumab (PACIFIC regimen).
- Unresectable, EGFR-mutated disease: cCRT followed by consolidation osimertinib.
- Unresectable, ALK-rearranged disease: cCRT and surveillance, with targeted ALK inhibition in subsequent lines rather than IO consolidation.[5,31]

STAGE IV

Oligoprogression

Within the spectrum of oligometastatic disease (OMD), the oligoprogression form is the most commonly encountered presentation during targeted therapy. The introduction of novel systemic agents has led to an increased incidence of oligoprogressive disease (OPD) in patients with advanced non–small cell lung cancer (NSCLC), particularly in the setting of acquired resistance following a prolonged tumor response to targeted therapies.[32] Oligoprogression is typically defined as disease progression in up to five sites following an initial response or disease stabilization with systemic therapy.[33] In this setting, the use of local ablative therapies, particularly SBRT, has emerged as a promising strategy to prolong systemic treatment benefit. By eradicating resistant tumor clones, local ablative therapy reduces tumor heterogeneity, with the primary objective of prolonging PFS2, defined as the interval until the development of new metastatic lesions, thereby extending progression-free survival and/or delaying the need to switch systemic therapy.[32] In a subset of patients (15–25%), this benefit may even translate into durable disease control.

Despite the low level of evidence, MDT has been adopted as a standard treatment in routine clinical practice and is recognized as the standard of care (SOC) in current guidelines.[6,34] The strongest data to date that supports use of local therapy in the management of OMD comes from experiences with NSCLC patient populations. Among the recent phase II studies summarized in Table 1, the HALT trial remains ongoing, and the SUPPRESS trial has been completed, with results pending. Of the trials that have reported data this year, the STOP trial failed to demonstrate a significant benefit but was heavily criticized for its highly heterogeneous patient population. [35] In contrast, the CURB trial [32] demonstrated that adding SBRT to systemic therapy in oligoprogressive NSCLC increased PFS nearly fourfold (from 2.2 to 10 months), leading to premature trial closure. Consequently, the impact of CURB on OS remains undetermined[36] (Table 4).

Another key insight gained from the CURB study is as follows: Beyond prolonging PFS, SBRT appears

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Table 5 Approximate half-lives of systemic agents relevant to SBRT–systemic therapy combinations

Drug	Target	T ½
Trametinib (Mekinist)	MEK1/2 inhibitor	~90–120 hour
Sunitinib (Sutent)	Multi-TKI	~40–60 hour
Osimertinib (Tagrisso)	3rd generation EGFR T790M	~48 hour
Gefitinib (Iressa)	1st generation EGFR tyrosine kinase inhibitor	~48 hour
Crizotinib (Xalkori)	ALK/ROS1 inhibitor	~42 hour
Afatinib (Giotrif)	2nd generation EGFR tyrosine kinase inhibitor	~37 hour
Erlotinib (Tarceva)	1st generation EGFR tyrosine kinase inhibitor	~36 hour
Alectinib (Alecensa)	2nd generation ALK inhibitor	~33 hour
Pazopanib (Votrient)	Multi-TKI	~30 hour
Lorlatinib (Lorbrena)	3rd generation ALK inhibitor	~24 hour
Nintedanib (Vargatef)	VEGFR/FGFR/PDGFR TKI	~10–15 hour
Axitinib (Inlyta)	VEGFR 1/2/3 inhibitor	~10 hour
Dabrafenib (Tafinlar)	BRAF inhibitor	~8 hour
Atezolizumab (Tecentriq)	Anti PD-L1	~27 day
Nivolumab (Opdivo)	Anti PD-1	~25 day
Pembrolizumab (Keytruda)	Anti PD-1	~22 day
Bevacizumab (Avastin)	VEGF inhibitor	~20 day
Durvalumab (Imfinzi)	Anti PD-L1	~18 day
Ipilimumab (Yervoy)	CTLA-4 inhibitor	~15 day
Ramucirumab (Cyramza)	VEGFR-2 monoclonal Ab	~14 day

to alter the pattern of disease progression in NSCLC patients. In patients managed with systemic therapy alone, progression often occurs at previously treated sites; however, in those receiving SBRT, durable local control is typically achieved, and subsequent progression tends to manifest at new metastatic sites.[32] This shift in progression dynamics underscores the biologic and clinical relevance of integrating SBRT into the management paradigm for oligoprogressive NSCLC.

In EGFR-mutated NSCLC, patients typically show a profound initial response to targeted systemic therapy; however, the development of resistance is inevitable, with disease progression often occurring around 18 months after treatment initiation. Encouragingly, approximately 70% of these progressions present as oligoprogression, creating an opportunity for local ablative strategies.[37] Evidence from a first prospective, randomized phase III SINDAS trial in EGFR-mutated patients with oligometastatic disease at diagnosis demonstrated that upfront SBRT combined with EGFR-TKI significantly improved both PFS (12.5months vs 20.2months (p<0.001)) and OS 17.4months vs 25.5months (p<0.001) compared to TKI alone.[38]

For patients treated with immune checkpoint inhibitors (ICIs), resistance more frequently manifests as polyprogressive disease.[39] However, in selected patients who are initially oligometastatic and later develop repeat oligoprogression following IO, local ablative RT has shown meaningful clinical benefit. In contrast, for patients with initially polymetastatic disease, even if oligoprogression emerges after IO, systemic therapy remains the preferred management approach.[40] Notably, in the setting of oligoprogression during IO, in a retrospective cohort study, the integration of local ablative RT has been shown to extend second progression-free survival (PFS-2) (17 versus 11.5 mo, HR 0.51, p=0.02) and may also confer an OS advantage (23 versus 13 mo, HR 0.40, p <0.001), reinforcing its role as a consolidative approach in carefully selected patients.[41]

Of course, while we are implementing these strategies, we are not entirely reassured — toxicity concerns remain substantial, and the lack of robust evidence or guideline support adds to this uncertainty. According to a consensus published by EORTC and ESTRO, thoracic RT administered in combination with ipilimumab, nivolumab, or CTLA-4/PD-1 inhibitor combinations is considered to carry a high risk of toxicity.[42]

In practice, we often attempt to pause systemic therapy during thoracic radiation to mitigate this risk. Among radiation oncologists, the fear of toxicity is significant, whereas medical oncologists are primarily concerned about tumor flare, which has been

Table 6 SBRT–systemic therapy combinations in lung cancer: Recommendations from the EORTC–ESTRO OligoCare consortium

Drug	Risk (%)	Drug administration on the same day with SBRT	Time interval	SBRT dose reduction	Use of more SBRT fr #
Anti-CTLA4 (ipilimumab)	11–20	No	No cycle omission At least a 1-week interval	No	No
Anti-PD-1/PD-L1	0–10	No	No cycle omission interval?	No	No
Anti-CTLA4 + anti-PD-1 (ipi-nivolumab)	>20	No	At least a 1-week interval before and after	No	No
EGFR X	0–10	No	?	No	No
ALK X	0–10	?	?	No	No
Anti-VEGF	11–20	No	One cycle should be omitted At least a 1-week interval before and after	No	No

Items in bold indicate consensus; items in italic indicate majority agreement. The risk of severe infield toxicity was categorised as: grade 3–5 toxicity of 0–10% was defined as low risk, 11–20% was defined as intermediate risk, and above 20% was defined as high risk. SBRT: Stereotactic body radiotherapy

reported in up to 23% of patients within a median of 8 days after treatment interruption.[43] This is far from a negligible risk, particularly in patients with systemic disease, where both the duration and timing of treatment breaks are critical. For this reason, decisions should always be made in close collaboration with medical oncology teams.

The administration of RT within five half-lives (5 t½) of a systemic agent is regarded as concurrent treatment, then—considering that the half-lives of these agents are provided in Table 5—avoiding true concurrency would necessitate an impractically long interval in routine clinical practice.

The consortium recommendations for the most commonly used agents in lung cancer emphasize several key points[42] (Table 6).

- Avoid administering the systemic agent on the same day as RT.
- Do not reduce the total dose or increase the number of fractions — RT should proceed as planned.
- Preferred treatment intervals:
  - o For ipilimumab or ipilimumab + nivolumab combinations, avoid skipping a cycle, but allow at least a one-week interval.
  - o For nivolumab monotherapy, there is no consensus on the ideal break period.
  - o For anti-PD-L1 agents, skipping one cycle and waiting at least one week is generally recommended, though longer intervals are sometimes used.
  - o For EGFR and ALK TKIs, there is no clear consensus either. However, in daily practice — given the longer half-lives of agents like osimertinib or crizotinib — we generally pause treatment for two days before and two days after RT. For TKIs with shorter half-lives, a one-day break before and after RT is commonly applied.
  - o For Anti-VEGF a consensus was reached that a minimum of one cycle should be omitted and SBRT should not be within one week of VEGF antibody administration. (However, in routine practice, a minimum interval of 2–3 weeks—typically longer than one week—is usually implemented).
  - o For Multikinase inhibitors there was a consensus that all multikinase inhibitors should not be administered on the same day as SBRT and an interruption for maximum of 2 weeks before or after the delivery of SBRT. But a no consensus was not reached on a minimum interval between delivery of other multikinase inhibitors and SBRT.

Brain metastases

The high intracranial efficacy of EGFR TKIs (CNS response rates are approximately 70%, CNS disease control rates approaching 90%), coupled with concerns about the potential neurological toxicity of RT, has reshaped treatment paradigms in patients with driver mutation–positive brain metastases. This has led to the adoption of a deferred RT strategy during systemic therapy, aiming to optimize intracranial disease control while minimizing treatment-related morbidity. However, the evidence supporting this approach remains limited and is primarily based on findings from observational studies rather than robust prospective comparisons with RT.

Turk J Oncol 2025;40(Supp 1):7–21
doi: 10.5505/tjo.2025.2

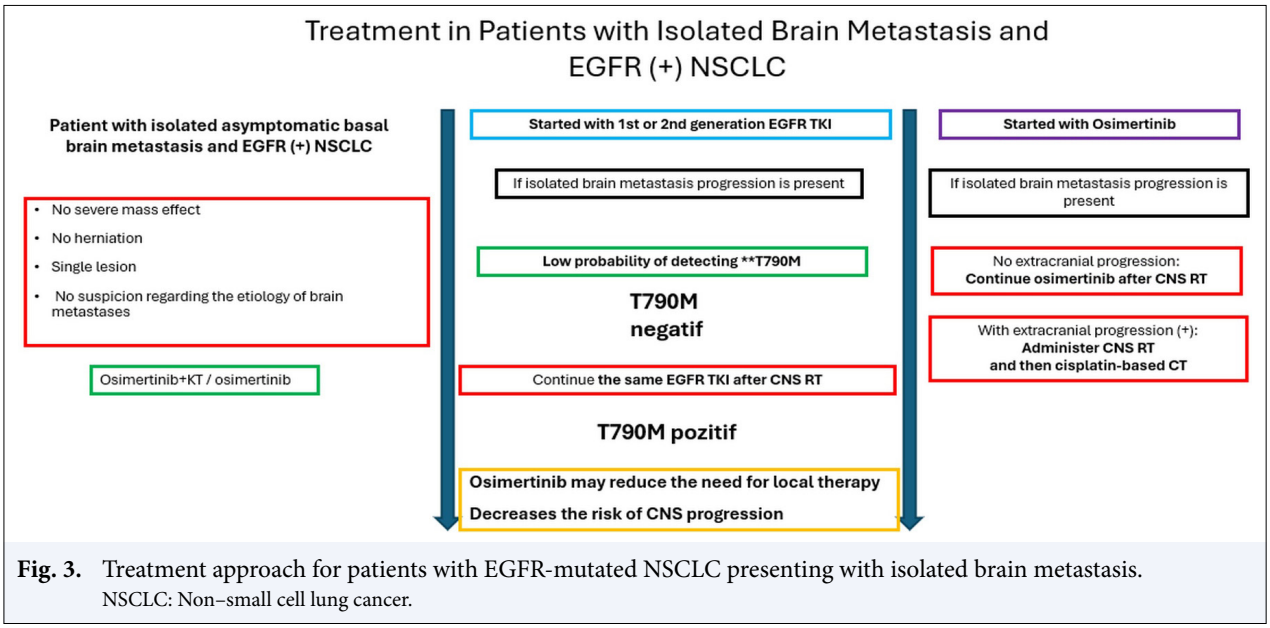

Fig. 3. Treatment approach for patients with EGFR-mutated NSCLC presenting with isolated brain metastasis.
NSCLC: Non–small cell lung cancer.

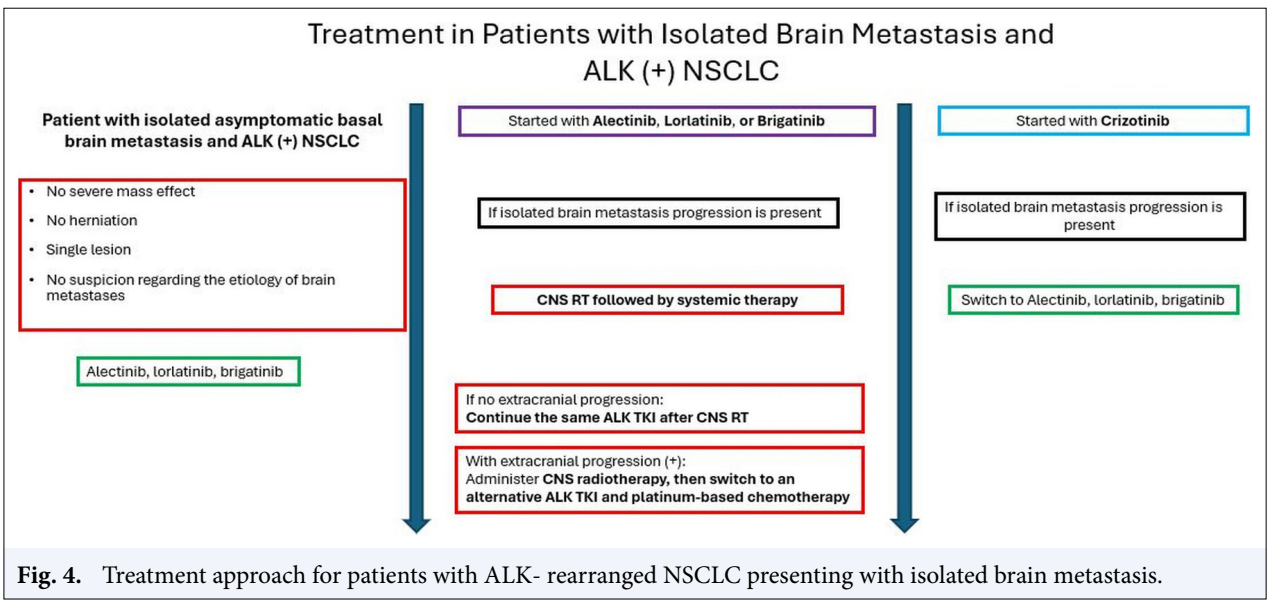

Fig. 4. Treatment approach for patients with ALK- rearranged NSCLC presenting with isolated brain metastasis.

For EGFR-mutated disease, if there is an isolated, asymptomatic brain metastasis that does not require surgery, treatment can be started directly with a third-generation agent such as osimertinib, and RT can be deferred. If a patient experiences intracranial progression while on osimertinib, local RT can be administered and systemic treatment with osimertinib can be continued.

For patients progressing on first- or second-generation EGFR TKIs, such cases are often considered functionally T790M-negative, as the progression typically results from pharmacokinetic resistance — insufficient CNS penetration of the drug leading to oligoprogression. In these scenarios, the likelihood of detecting a T790M mutation is considerably lower compared to extracranial progression. In such cases, local brain RT can be performed while continuing the same systemic agent. However, if T790M testing has been performed by biopsi, switching to osimertinib while deferring local RT can also be considered (Fig. 3).

For ALK- rearranged disease, a similar approach applies. If the patient is asymptomatic and surgery is not required, treatment can be initiated with a second- or third-generation ALK TKI. Since first-generation crizotinib has no meaningful CNS penetration, patients

initially started on crizotinib should be switched to a second- or third-generation agent, with RT deferred.

If brain-only progression occurs while on a second- or third-generation ALK TKI, or if, after 1–3 months of second-generation EGFR TKI therapy, the lesion demonstrates less than a 30% reduction in size, local RT can be administered while continuing the same systemic therapy.[1] (Fig. 4).

Future Directions

The treatment landscape for NSCLC is becoming increasingly complex. Future studies will likely refine response-adapted strategies, including the escalation or de-escalation of adjuvant therapy based on pathological or molecular response. Biomarker-driven adaptive approaches may help identify patients who can safely discontinue therapy or those who require intensified treatment to optimize long-term outcomes. Assessing the feasibility of converting unresectable disease into resectable disease constitutes one of the most significant study paradigms for the near future.[5]

CONCLUSION

Modern systemic therapies have reshaped curative-intent and advanced-stage management in NSCLC, but their full value depends on thoughtful integration with RT.

For resectable disease, molecular selection directs adjuvant targeted therapy (osimertinib, alectinib) or peri-operative chemo-immunotherapy; for unresectable stage III, durvalumab consolidation or, in EGFR-mutated tumors, consolidation osimertinib, defines current standards.

In oligoprogression, judicious use of SBRT can extend systemic control prolong PFS2; in brain metastases, the intracranial potency of new generation TKIs supports deferred RT in carefully chosen patients. Pragmatically, clinicians should prioritize early comprehensive testing (EGFR, ALK, PD-L1), employ multidisciplinary tumor boards to adjudicate resectability and timing, initiate consolidation therapy promptly once acute toxicities resolve, and individualize RT fields/doses while adhering to ALARA principles. Future directions should prioritize response-adapted pathways, biomarker-guided de-escalation or escalation, along with optimizing the duration and sequencing of systemic and RT. Collectively, these developments highlight the need for multidisciplinary management and personalized treatment planning in the era of combined-modality therapy.

Conflict of Interest Statement: The author have no conflicts of interest to declare.

Funding: The author declared that this study received no financial support.

Use of AI for Writing Assistance: No AI technologies utilized.

Peer-review: Externally peer-reviewed.

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