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Evolution of systemic therapy for stages I–III non-metastatic non-small cell lung cancer

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Abstract

The treatment goal for patients with early stage lung cancer is cure. Multidisciplinary discussions of surgical resectability and medical operability determine the modality of definitive local treatment (surgery or radiotherapy) and associated systemic therapies to further improve the likelihood of cure. Trial evidence supports cisplatin-based adjuvant therapy either after surgical resection or concurrently with radiotherapy. Consensus guidelines support neoadjuvant chemotherapy in lieu of adjuvant chemotherapy and carboplatin-based regimens for patients who are ineligible for cisplatin. The incorporation of newer agents, now standard for patients with stage IV lung cancer, into the curative therapy paradigm has lagged owing to inefficient trial designs, the lengthy follow-up needed to assess survival end points, and a developmental focus on the advanced-stage disease setting. Surrogate end points such as pathologic response are being studied and might shorten trial durations. In 2018, the anti-PD-L1 antibody durvalumab was approved for patients with stage III lung cancer after concurrent chemoradiotherapy. Since then, the study of targeted and immunotherapies in patients with early stage lung cancer has rapidly expanded. In this Review, we present current considerations for treating patients with early stage lung cancer, and explore the current and future state of clinical research to develop systemic therapies for non-metastatic lung cancer.

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Author contributions

All authors researched data for article, made substantial contributions to discussions of content, wrote the manuscript, reviewed and edited the manuscript before submission.

The authors of this Review present current considerations for treating patients with early stage lung cancer, discussing the critical determination of resectability by thoracic surgical oncologists and the management of both resectable and unresectable disease with a focus on systemic therapy selection. They also address innovations in drug development, trial design and efforts to identify early stage cancers.

Introduction

Over the past 60 years, the development of systemic therapies for non-metastatic lung cancer has been hampered by disease heterogeneity, patient comorbidities, and a lack of safe, tolerable and effective drug therapies. Compared to patients with breast or colon cancer, individuals with lung cancer tend to be older on average, and are predominantly cigarette smokers with high rates of emphysema and heart disease leading to higher all-cause mortality and debility caused by surgery (especially pneumonectomy)[1]. Combined, these factors reduce the tolerability of cytotoxic drugs, which have been the best option for these patients until the past decade. Further challenges in the development of systemic therapies for non-metastatic lung cancer include the fact that one-third of patients are diagnosed at stages in which multimodality therapy is indicated[2], and that studies requiring an overall survival (OS) end point take decades to complete.

The demographics of patients with lung cancer have changed in the past decade[3–5], with decreases in smoking prevalence, a lower stage at diagnosis, and improved pre-operative staging (using ^{18}F-fluorodeoxyglucose (FDG)-PET and MRI of the brain). With further implementation of lung cancer screening, we hope that a stage migration to earlier stages of disease at diagnosis will also be seen. Refinements of surgical techniques have advanced such that, stage for stage, the survival of patients treated with surgery alone is steadily improving[6,7], and morbidity following surgery has been reduced[8,9]. Similarly, radiotherapy techniques have improved, resulting in higher conformality of the radiation fields targeting the tumour and markedly decreased toxicities with intensity-modulated radiation therapy (IMRT) compared with 2D or 3D techniques[10]. Proton therapy and MRI-guided radiotherapy have the potential to further improve dose delivery. Systemically, the arsenal of agents used to treat metastatic NSCLC has also expanded dramatically, with the targeting of mutant oncogenes by tyrosine-kinase inhibitors (TKIs) and the use of monoclonal antibodies to block immune checkpoints[11]. A multitude of agents are now approved by the FDA for the treatment of patients with advanced-stage lung cancers (Fig. 1). This large number of options contrasts starkly with the limited number of drug indications in the guidelines for non-metastatic NSCLC. The successes of newer therapies in the advanced-stage setting, including patients without disease progression ≥5 years after diagnosis[12], presents the extraordinary opportunity to expand the use of these agents to personalize care for individuals with non-metastatic cancers to enhance their chances of remaining relapse free from the lung cancer being treated and, ultimately, cured.

This Review explores the essential considerations for the management of patients with non-metastatic NSCLC. We discuss the critical determination of resectability by thoracic surgical oncologists and the management of both resectable and unresectable disease with a

focus on how systemic therapy selection has changed. Finally, we present how innovations in drug development, trial design and efforts to identify early stage cancers through lung cancer screening have reinvigorated a historically barren research landscape and prompted clinicians to re-imagine the care of patients with potentially curable lung cancer.

Surgical considerations

The thoracic surgeon's decision to offer surgery in the management of non-metastatic NSCLC depends on both the tumour extent and its relationship to surrounding structures (technical resectability) and the extent of the surgery needed to completely remove the tumour in the context of patient fitness (medical operability). If the tumour is not completely resectable or the patient is not medically operable, the patient is referred for definitive non-surgical management with radiotherapy, as discussed in the next section.

Technical resectability

Technical resectability is assessed by the thoracic surgical oncologist who evaluates imaging to determine whether complete resection of the tumour and regional lymph nodes (R_0 resection) is possible. Resectability of stage I and II tumours is usually defined by review of preoperative imaging. By contrast, the criteria for resectability of stage III tumours are more complex, defined by tumour characteristics (size or invasion) or the extent of N2 nodal involvement and relationship of the tumour to the airways and vasculature. Tumour characteristics, for example invasion of the vertebral bodies or brachial plexus, sometimes require involvement of a neurosurgeon as part of the multidisciplinary team. Nodal involvement can be estimated through the use of non-invasive imaging such as CT and PET, but is more accurately determined by invasive mediastinal staging using endobronchial ultrasound[13] and mediastinoscopy. The number and location of lymph nodes that enter into the resectability decision varies by region, centre and surgeon. General agreement exists that confluent bulky lymph nodes should not be considered as resectable, whereas a single station involvement is accepted to be resectable in all guidelines[11,14,15]. No consensus exists on the number of involved mediastinal lymph node stations that make an R_0 resection unlikely. In some centres, studies have shown promise using neoadjuvant cytotoxic chemotherapy to induce conversion of borderline resectable NSCLC to resectable NSCLC; however, this approach is not considered standard[16,17]. We anticipate that such an approach will gain momentum as regimens with improved efficacy are moved into the non-metastatic setting.

Medical operability

Medical operability is generally determined by cardiac and pulmonary fitness. Cardiac fitness is required for general anaesthesia and the stresses of surgery and postoperative recovery. Pulmonary fitness is defined by pulmonary function testing[18], including diffusion capacity[19,20], ventilation–perfusion imaging, and, at times, cardiopulmonary exercise testing[21,22]. Poor pulmonary function can prohibit a surgery, although occasionally, borderline pulmonary function can remain stable or improve postoperatively if a volume reduction following surgery positively affects respiratory mechanics.

Both technical resectability and medical operability should be determined by a multidisciplinary team at the time of diagnosis and staging to assign a treatment plan. If the tumour grows through neoadjuvant therapy or the patient has interval medical events or complications of therapy, both resectability and operability might need to be redetermined after completion of neoadjuvant therapy.

Unresectable or inoperable disease

For most patients deemed to have medically inoperable stage I and II, node-negative NSCLC, standard therapy is definitive stereotactic body radiation therapy (SBRT; also known as stereotactic ablative body radiation) to a biologically effective dose ≥100 Gy[11]. Rarely, SBRT is not possible in patients with large primary tumours, central tumours and some other conditions, such as interstitial lung disease, for which the risks of SBRT are unknown. With this approach, long-term local control rates of the treated primary tumour are 90–95%, with nodal and systemic progression-free survival (PFS) of 70–80%[23–26]. Systemic therapy can be difficult to administer to these patients owing to frailty, age, and the medical comorbidities that rendered them inoperable. Although patients with larger or more FDG-avid tumours are at increased risk of intrathoracic, nodal and systemic disease progression, the role of systemic anticancer therapy in these patients has not been defined[27–29].

Concurrent chemotherapy and radiation therapy

Definitive concurrent chemotherapy and radiation therapy (cCRT; typically to a total dose of 60–66 Gy in 30–33 fractions) followed by 1 year of durvalumab is the standard of care for patients with unresectable, locally advanced, node-positive (stage IIB–IIIC) NSCLC[11,30,31]. Prior to 2018, the standard of care for patients with unresectable locally advanced-stage NSCLC was treatment with cCRT to a total radiation dose of 60 Gy in 30 fractions[32], although these patients had poor outcomes largely driven by poor distant control[32]. Multiple failed attempts were made to improve upon this regimen with intensification of systemic therapy and escalation of the radiation dose[33–35]. RTOG 0617 explored whether 74 Gy in 37 fractions was superior to the standard dose of 60 Gy in 30 fractions, but treatment with 74 Gy was associated with reduced OS and poorer local control[36,37]. The addition of cetuximab to weekly carboplatin and paclitaxel only added toxic effects. Cisplatin and pemetrexed were also tested. In a study published in 2016[38], cisplatin and pemetrexed did not improve OS, however this regimen is often adopted in clinical practice owing to the milder adverse effects of this combination relative to cisplatin and etoposide[11,38].

Immunotherapy

The PACIFIC trial established a new standard of care by investigating the addition of durvalumab (an anti-PD-L1 monoclonal antibody) following cCRT[30], consisting of at least two cycles of platinum-based doublet chemotherapy delivered concurrently with definitive radiotherapy to a total dose of 54–66 Gy. Patients without disease progression after cCRT were randomly assigned 2:1 to receive either durvalumab or placebo. Durvalumab was initiated within 42 days from the end of cCRT. Durvalumab improved median PFS by 11 months[31] and median OS by 18.4 months[39]. The study was stratified by patient age, sex, and smoking history, but not tumour PD-L1 expression. Preplanned subset analyses did

include PD-L1 expression at a 25% threshold, with benefit seen in both subsets. However, an unplanned retrospective analysis found that durvalumab did not improve OS in a subgroup with PD-L1 expression of <1%[40]. Grade 3 or 4 pneumonitis rates were comparable between the study arms[31]. A broad exploration of intrathoracic versus extrathoracic failures demonstrated that consolidative durvalumab reduced the sites of first progression in both intrathoracic and extrathoracic sites compared with placebo[41]. Interestingly, first progression most commonly occurred in intrathoracic sites; historically, the greatest risk in patients treated for locoregional disease has been distant metastatic failure. The observation of common intrathoracic progression in the setting of improved systemic control begs the question of whether optimized intrathoracic tumour control by optimized radiation plans or surgery in resectable cases might be able to further improve outcomes.

Building on the success of immunotherapy following cCRT, multiple efforts are taking place to expand the role of immunotherapy in unresectable NSCLC. Even patients with stage I NSCLC remain at a 20–30% risk of progression and death[8]. Studies have been initiated to add adjuvant immunotherapy after definitive SBRT for node-negative stage I NSCLC. Some studies are focusing on patients with larger tumours (≥2 cm diameter) or higher standardized uptake values (≥6.2)[42]; others include patients with broader criteria[43]. Trials are also examining the duration of adjuvant immunotherapy (up to 6 months in SWOG S1914[44] versus 24 months in PACIFIC-4[43]), initiation of immunotherapy relative to SBRT (two cycles before SBRT in SWOG S1914[44] versus after SBRT in PACIFIC-4[43]), placebo control arm (only PACIFIC-4), as well as type and dosing of immunotherapy agents.

PACIFIC-2 (REF.[45]) is a randomized, double-blind, phase III trial investigating the use of concurrent durvalumab (1,500 mg) every 4 weeks with cCRT compared to placebo and cCRT. This study is enrolling patients prior to cCRT and will thus provide much needed detail on the chemotherapy and radiotherapy parts absent from the PACIFIC trial. The comparator arm of this trial is cCRT alone, rather than the current standard of care of cCRT followed by consolidative durvalumab. Dual immune-checkpoint inhibition with ipilimumab plus nivolumab with cCRT is being explored and compared to nivolumab with cCRT or durvalumab with cCRT in the phase III trial CheckMate73L (REF.[46]).

The search continues to develop therapies for patients who are not candidates for cCRT because of comorbidities precluding them from undergoing cCRT, including frailty or tumour extent. These patients are typically treated with sequential CRT or RT alone. PACIFIC-6[47] is a phase II study investigating the addition of durvalumab after sequential CRT in this patient subgroup.

Although the studies so far have focused on immunotherapy, efforts are being made to add targeted therapy after definitive cCRT. The LAURA[48] study is the first to prescribe adjuvant osimertinib or placebo to patients with *EGFR*-mutated NSCLC following cCRT.

Lastly, improvements in radiotherapy techniques will likely further decrease radiation-related toxicities, a concern when radiation is combined with novel systemic therapies. Radiation doses to the lungs[49,50], heart[37,51], great vessels[52], oesophagus[50,53,54], and circulating lymphocytes[55–58] have been correlated with the risks of pneumonitis, esophagitis

and decreased survival. Proton therapy offers considerable potential in minimizing doses to at-risk organs, especially in patients with extensive disease involvement (for example, of the bilateral mediastinum, supraclavicular fossae or lower lobes of the lungs (Fig. 2)). RTOG 1308 (REF.[59]) is a phase III trial comparing photon and proton radiotherapy as part of cCRT with durvalumab.

Adjuvant therapy for resected NSCLC

More than 50% of patients experience recurrence after surgery alone[8]. In patients with resected disease, the most accurate prognostic factor is pathologic stage[8]. The best way to risk-stratify a lung cancer population prior to enrollment in an adjuvant drug trial is pathologic assessment of the resection specimen and pathologic stage, the gold standard. Using surgical pathology and pathologic stage, an accurate assessment of the risk of recurrence is possible[60,61]. Adjuvant therapy is prescribed based on stage and patient fitness. The use of additional predictive biomarker testing for the precise assignment of adjuvant therapy has yet to make its way into routine clinical practice, although we anticipate routine testing for *EGFR* mutations based on the recently reported results of a trial of adjuvant osimertinib[62].

Chemotherapy

Following successful surgery, randomized controlled trials of patients with stages I–III NSCLC have demonstrated that postoperative, cisplatin-based therapy significantly reduces the risk of death, especially in stage II and III disease[63]. The efficacy of cytotoxic therapy has been established by two fundamental approaches: 1) intense, toxicity-limited, two-drug, cisplatin-based combinations delivered intravenously over a few months to eliminate micro-metastatic disease[64]; or 2) prolonged 1–2 year delivery of oral antimetabolites (uracil–tegafur) to suppress cancer growth[65]. Dose-intense cytotoxic approaches are limited by issues of tolerance and safety. Clear evidence exists that benefits are often outweighed by harms, or inability to deliver the planned therapy. For example, clinical trials using cytotoxic three-drug regimens or in which high numbers of patients also received postoperative radiotherapy (PORT) were unable to demonstrate benefit, whereas studies that used lower-dose cisplatin-based doublet regimens in patients without N2 disease were successful[66,67]. Although PORT does not interfere with the benefit of cytotoxic chemotherapy[68], data from 2020 raise concerns that PORT can increase the risk of non-cancer death[69]. Of note, highly toxic adjuvant chemotherapies also increase the risk of non-cancer death, and are clearly more harmful than helpful for patients with low-risk (stage IA) cancers[64,70]. By contrast, prolonged treatment with antimetabolites is well-tolerated and can be effective, even for patients with stage I disease[71,72]. However, clinical trials demonstrating the benefit of prolonged therapy with uracil–tegafur have not been replicated outside of Japan owing to issues of drug availability and practice preferences in the rest of the world.

The current approach to adjuvant cytotoxic chemotherapy is to take into account a combination of pathologic stage and a medical assessment of the patient, balance the benefits and harms, and proceed with treatment as a shared decision with individuals who are willing to take on additional adverse effects and risk. For example, meta-analyses

have shown that four cycles of cisplatin-based, two-drug combinations lower the risk of death by 20% (relative risk reduction) compared with surgery alone in patients with pathologic stage II and III NSCLC[64]. Given that the risk of cancer-related death in this population is high with surgery alone (50–80%), the absolute risk reduction is also high (10–16%)[64]. This absolute risk reduction is balanced against the risks associated with cytotoxic chemotherapy as adjuvant therapy after complete surgical resection: death (1%, typically related to neutropenic sepsis)[74], permanent hearing loss or kidney damage (3–5%), nausea (common) and fatigue (nearly universal)[73–75]. Advanced patient age does not predict benefit from cisplatin but does predict increased risk of treatment-related toxicity[76]. As the age of patients with newly diagnosed NSCLC is increasing, cisplatin-based therapy is often not an acceptable option.

The benefit of adjuvant cisplatin doublets with etoposide or vinorelbine took decades to establish[34,64,67]. To avoid multi-decade trials in the United States, expert consensus alone has been sufficient to establish newer regimens combining cisplatin with pemetrexed, gemcitabine or docetaxel.[11] In Japan, a clinical trial of cisplatin with pemetrexed versus vinorelbine in patients with resected lung adenocarcinoma was done for regulatory approval of pemetrexed in this setting. The study failed to show superiority of pemetrexed but confirmed a reduced toxicity profile[77]. US guidelines recommend pemetrexed in this setting[11]. Also backed by expert consensus is the common practice to use carboplatin instead of cisplatin in patients with medical contraindications to cisplatin, such as hearing loss or renal insufficiency[78]. Adding drugs with different mechanisms of action, such as angiogenesis inhibitors and cancer antigen-targeted vaccines, to cisplatin-based adjuvant treatments has not improved outcomes in prospective studies[73,79]. However, numerous new drugs with activity in the treatment of advanced-stage NSCLC are worthy of study (Fig. 1).

Targeted or immunotherapy

In metastatic NSCLC, cytotoxic chemotherapy has been replaced with targeted therapy or immunotherapy in biomarker-selected populations[80,81]. However, evidence is currently lacking to replace chemotherapy in the curative adjuvant setting[82]. Incorporation of platinum-based therapy has been either a mandate or an option in most trials looking to register new drugs in the adjuvant setting in non-metastatic NSCLC (Table 1). None of these adjuvant studies yet has mature data. However, the ADAURA study, in which patients with completely resected NSCLC received adjuvant osimertinib or placebo for 3 years after completion of standard of care adjuvant chemotherapy, reported a striking improvement in disease-free survival (DFS) (hazard ratio (HR) 0.17; 95% CI 0.12–0.23) in patients with resected stage II–III *EGFR*-mutated NSCLC[62]. ADAURA is the first biomarker-selected adjuvant study anticipated to change the standard of care in resected lung cancer. The results of the other listed adjuvant TKI and immunotherapy studies are eagerly anticipated.

Neoadjuvant therapy

Chemotherapy

In 2005, the survival results of the decade-long adjuvant studies presented above[67,83] led to early closure of concurrently running neoadjuvant trials because these trials did not

include an adjuvant component and adjuvant chemotherapy was the new standard of care. Therefore, few completed phase III studies are available to guide neoadjuvant therapy. Results from meta-analyses evaluating the use of neoadjuvant[70] or adjuvant[64] platinum doublet chemotherapy in patients with resectable stage IB–IIIA NSCLC concluded that both approaches yield an absolute benefit in 5-year OS of approximately 5% (HR 0.87 for pooled neoadjuvant studies; HR 0.89 for the adjuvant studies; both hazard ratios are for therapy versus surgery alone). As a result, the guidelines support the use of neoadjuvant platinum-based chemotherapy in patients with clinical stages that would merit adjuvant chemotherapy[11]. Neoadjuvant treatment offers several advantages over adjuvant therapy, including improved patient tolerance prior to surgery[84], tumour downstaging[85], an earlier opportunity to eradicate micrometastases, and more rapid assessment of therapeutic efficacy either before surgery with scans or at the time of resection[86]. Neoadjuvant approaches have the additional advantage of permitting a change in systemic treatment either preoperatively based on imaging results[87] or postoperatively, based on pathologic assessment of the resection specimen. Neoadjuvant therapy also provides an opportunity to evaluate surrogate markers of clinical efficacy that might correlate with improved survival[88].

Immunotherapy

Immune-checkpoint inhibitors targeting CTLA4, PD-1 and its ligand PD-L1 have changed the treatment landscape for patients with advanced-stage NSCLC[89]. Immunotherapy in the neoadjuvant setting has the hypothesized advantage of priming an anti-tumour response and imparting immunological memory early in the disease process[90]. This strategy provides unprecedented opportunities to advance care and for translational work. Elevated neoantigen burden and reduced neoantigen heterogeneity are associated with longer survival in patients with early stage NSCLC[91], suggesting that the neoadjuvant setting might represent the optimal time point to achieve the maximal clinical benefit of immunotherapy. Two doses of neoadjuvant nivolumab (anti-PD-1) produced a 45% complete or major (≤10% viable tumour cells) pathologic response (MPR) rate in 20 resected tumours[92]. In the multicenter Lung Cancer Consortium 3 (LCMC3) study[93], neoadjuvant atezolizumab (anti-PD-L1) produced a 19% MPR rate[94], comparable to cisplatin-based neoadjuvant chemotherapy in earlier studies. In 2020, a neoadjuvant study evaluating the PD-1 inhibitor, sintilimab, in 37 Chinese patients with resectable NSCLC reported an MPR rate of 41%[95]. While the results of all of the aforemented neoadjuvant immunotherapy trials are intriguing, few pathologic complete responses (pCRs) were seen and no robust predictive biomarker for response was identified. Reported results of the phase II randomized NEOSTAR study evaluating neoadjuvant nivolumab or nivolumab plus ipilimumab in patients with resectable NSCLC reported a 38% MPR rate with the combination regimen in 21 treated patients, most of these pCRs[96].

Combination immunotherapy and chemotherapy

Combining immunotherapy with chemotherapy in the perioperative setting might further increase clinical efficacy. Indeed, chemotherapy might synergize with immunotherapy by killing tumour cells, improving the T cell:cancer cell ratio, reducing immunosuppressive substances released by the tumour, and releasing antigens for presentation, thereby expanding the anti-tumour response[97]. Chemotherapy also stimulates PD-L1 expression

in NSCLC[98]. The addition of immunotherapy to chemotherapy improved outcomes of patients with metastatic NSCLC[89,99–101], encouraging the investigation of the combination strategy in the preoperative setting. In resectable NSCLC, atezolizumab plus carboplatin and nab-paclitaxel produced an MPR in 57% (95% CI 37–75%), including pCRs in 33% (95% CI 19–51%) of 30 patients[102]. In the phase II NADIM study, neoadjuvant nivolumab plus carboplatin and paclitaxel induced MPR in 34 (83%; 95% CI 68–93%) of 41 patients with resected stage IIIA (N2) NSCLC, of whom 26 (63%; 95% CI 62–91%) had a pCR[103]. The 18-month OS in NADIM was 93.5%[103]. The SAKK single-arm study of durvalumab and chemotherapy in patients with stage IIIA (N2) NSCLC showed comparable pathologic remission rate results[104]. The results of these studies have prompted multiple randomized phase III studies of neoadjuvant chemotherapy with or without immunotherapy (Table 2). We anticipate the readout of pathologic end points to some of these studies within the next year[105].

In advanced-stage disease, biomarker-matched molecular therapies are better tolerated than chemotherapy and can produce response rates that exceed 50%[106]. Initial studies of neoadjuvant targeted therapies are promising. The EMERGING/CTONG1103 trial demonstrated that neoadjuvant erlotinib produced an MPR in 10% of patients with stage IIIA-N2 *EGFR*-mutated NSCLC; this result compares with a 0% MPR in the neoadjuvant chemotherapy arm[107]. The NeoADAURA phase III trial comparing neoadjuvant osimertinib versus chemotherapy versus the combination is planned for patients with *EGFR*-mutated lung cancer[108]. Finally, the Lung Cancer Mutation Consortium has proposed an umbrella trial for resectable (stages IB–IIIB) NSCLC that will identify 10 actionable oncogenic drivers at diagnosis and match patients with corresponding neoadjuvant targeted therapies[86].

Clinically, neoadjuvant therapy has many advantages over adjuvant therapy to both the patient and the treating clinician. The results of the neoadjuvant therapy studies suggest that their promise will be realized for correlative science as well. We are hopeful that the results of the phase III neoadjuvant studies in progress will demonstrate both the theoretical advantage of improved efficacy to immunotherapy with the tumour *in situ* and the prospect of earlier trial readouts based on pathologic end points that serve as surrogates for clinical outcomes.

Trimodality therapy

Trimodality therapy in resectable NSCLC refers to the use of systemic therapy, radiotherapy and surgery. To date, no level 1 evidence exists to support trimodality therapy in most patients with resectable NSCLC. Three scenarios remain in which trimodality therapy is considered: induction chemoradiotherapy for superior sulcus tumours, PORT for resected N2 disease, and induction chemoradiotherapy for resectable N2 disease[11].

Induction chemoradiotherapy

Induction chemoradiotherapy followed by surgery and adjuvant therapy for tumours of the superior sulcus (Pancoast tumours) remains a standard of care based on the findings of the Intergroup Trial 0160, a single-arm study that showed superior outcomes in patients who received induction cisplatin plus etoposide plus radiotherapy to 45 Gy compared to historic

controls of surgery or radiotherapy alone[109,110]. With the identification of more effective and better tolerated systemic therapies, some now advocate for induction chemotherapy only in patients with Pancoast tumours, reserving radiotherapy for the postoperative setting where persistent or bulky disease can be more precisely targeted[111].

Induction chemoradiotherapy for patients with resectable N2 disease without Pancoast tumours remains a therapeutic option in the NCCN guidelines and is considered a standard of care by many of the NCCN institutions[11]. The accumulated data shows that preoperative chemoradiotherapy is associated with more toxicity and no improvement in resection rates or survival over induction chemotherapy alone[112,113].

Postoperative radiotherapy (PORT)

PORT to the mediastinum for patients with resected NSCLC involving the N2 lymph nodes has been considered a therapeutic option based on findings from multiple database studies and subgroup analyses of adjuvant chemotherapy treatment trials[114–117]. These studies show a clear improvement in local control and a 5% improvement in OS with PORT to 50–54 Gy in patients with completely resected N2 disease. The results of the phase III Lung ART study, a prospective, randomized trial of PORT were presented at the 2020 ESMO Congress[69]. The study was designed to show a 10% improvement in DFS at 3 years. This study failed to meet its prespecified primary end points, which was not surprising as retrospective studies have shown only a 5% survival advantage at 5 years. An increase in non-cancer-related deaths in the radiation arm of the Lung ART study again raise doubts about the overall benefit of trimodality therapy[69].

Trial design

The pace of progress in early stage resectable NSCLC has been slowed by the long time required for data maturity when drugs are studied in the adjuvant setting. Although surgical pathology and surgical staging enables accurate study inclusion and stratification, the duration of follow-up necessary for clinical outcomes is nearly a decade long, as illustrated by the National Clinical Trial Network's ALCHEMIST study platform evaluating adjuvant erlotinib for patients with resected *EGFR*-mutated NSCLC and adjuvant crizotinib for patients with resected *ALK*-rearranged NSCLC[118]. These trials of TKIs opened in 2014 and neither is fully enrolled, likely owing to the rarity of patient populations in the United States, a lack of routine clinical biomarker testing, and the toxicity profiles of the drugs. Both drugs are no longer the agents of choice for their respective diseases and, already, another placebo-controlled trial of adjuvant osimertinib has demonstrated a substantial benefit in DFS with very few treatment discontinuations as a result of toxicity[62], making the ALCHEMIST outcomes related to targeted therapy, once available, of questionable relevance. The rapid pace of advancements in systemic therapy in metastatic NSCLC (Fig. 1) cannot be reasonably replicated in the adjuvant space. Two trial paradigms might accelerate progress. The first is neoadjuvant investigation with evaluation of pathologic end points as surrogates for later clinical end points. The second is utilization of predictive biomarkers for risk enrichment to select the adjuvant population at highest risk — the group

most in need of better adjuvant therapies and most likely to provide a demonstration of benefit with the fewest patients in the shortest time.

Surrogate end points

Surrogate end points are objective and reproducible measures that result from study intervention. As per regulatory authorities in the US, accelerated approval can be considered based on a surrogate end point that is reasonably likely to predict the traditional clinical end point[119]. DFS has been statistically validated as a surrogate end point for OS in a meta-analysis of trials of surgery or radiotherapy and chemotherapy in patients with non-metastatic NSCLC[120]. Whether this association is valid when evaluating mechanistically distinct drugs such as immunotherapies or targeted therapies is unclear. The controversy of using DFS as an appropriate end point has been reignited by the ADAURA data, which showed that patients treated with osimertinib had marked improvement in DFS compared with patients receiving placebo[62]; however, a co-primary OS end point was not included in the trial. Thus, whether TKIs will improve cure rate or just delay recurrence is unknown. The lack of data on whether the DSF advantage with adjuvant TKIs will translate into an OS advantage has sparked sharp debate over the use of osimertinib in the adjuvant setting, and many skeptic investigators await longer follow-up and the secondary OS end point results.

Pathologic response can also be used as a surrogate end point with neoadjuvant systemic therapy. Owing to its rarity after treatment with chemotherapy or single-agent immunotherapy, the use of pCR as a surrogate end point after induction cisplatin-doublet chemotherapy followed by surgery in patients with non-metastatic NSCLC was not useful[121]. A more clinically relevant frequency of events was seen when the potential surrogate event was defined as MPR (≤10% viable tumour cells). MPR to neoadjuvant chemotherapy occurred in 19% of patients, and OS and DFS were prolonged in patients who achieved MPR compared with patients who had >10% viable tumour cells after neoadjuvant chemotherapy (5-year OS 85% versus 40%, P <0.0001; 5-year DFS 78% versus 35%, P <0.001)[121]. The positive association between MPR and clinical outcomes in patients with resectable NSCLC has been reproduced in phase II studies of neoadjuvant chemotherapy[122] and chemotherapy plus anti-angiogenic therapies[123,124], which illustrates how MPR facilitates the rapid evaluation of neoadjuvant therapies[88]. Consequently, MPR has been proposed and adopted as an end point of interest in many neoadjuvant clinical trials in patients with resectable NSCLC, including those evaluating immunotherapies[125]. Furthermore, a standardized approach for MPR determination by pathologists across studies has been described[86,126]. However, prospective validation of pCR or MPR as a surrogate end point in lung cancer is pending completion of several studies (Table 2).

Most immunotherapy adjuvant studies in completely resected NSCLC (Tables 1 and 2) have completed enrollment, and the current trial landscape in early stage NSCLC has moved towards neoadjuvant investigation. However, many patients are pathologically upstaged at the time of surgery and adjuvant investigation remains important. Studies have demonstrated that the presence of circulating tumour DNA (ctDNA) following definitive treatment is associated with a high risk of disease recurrence[127]. Next-generation study proposals have been made to use this prognostic factor to select a high-risk patient population for adjuvant

investigation[128]. NCT04385368 (Table 1, REF.[129]) is the first phase III study to select a high-risk population of patients with completely resected non-metastatic NSCLC based on the persistence of ctDNA after surgery. This strategy offers escalation of care in patients at increased risk of recurrence and can enable clinical end points to be reached more quickly.

Conclusions

Systemic therapy for non-metastatic lung cancer continues to evolve. The durvalumab trial following cCRT in patients with unresectable lung cancer[30,40] was the first of many studies expected to alter routine care and improve the prognosis of individuals with local but still potentially lethal disease. We are now seeing biomarker testing of resected specimens and adjuvant osimertinib enter the clinic for patients with resected *EGFR*-mutated tumours[62]. However, the attitudes of the thoracic oncology community must evolve as have our therapies. We must revisit our opinions that the current survival rates for any patients with early stage lung cancer are acceptable[8]. Innovative clinical trials are needed to bring the personalized advances (Figure 1), which are now routinely applied to patients with stage IV disease, to patients with curable lung cancers.

We know that the earliest targeted therapy approvals for NSCLC have been associated with improvement in survival rates for patients with stage IV lung cancer diagnosed between 2013 and 2016[130]. Immunotherapy is poised to further alter these survival expectations. The important questions about the incorporation of immunotherapy and targeted therapy into the non-metastatic setting will focus on whether drugs should be given in sequence or combination, whether neoadjuvant or adjuvant therapy is preferable, and the optimal duration of therapy. Over time, the survival curves for all patients should continue to shift upwards. Our experiences with new therapies for individuals with metastatic lung cancers assure us that it will.

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Competing interests

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Key points

- Cisplatin-based adjuvant chemotherapy remains the standard of care for patients with resected high-risk non-metastatic non-small cell lung cancer (NSCLC).
- Anti-PD-L1 therapy with durvalumab after concurrent chemotherapy and radiotherapy for unresectable or inoperable non-metastatic NSCLC improves overall survival.
- Osimertinib for 3 years after standard adjuvant therapy improves disease-free survival in patients with NSCLC harbouring *EGFR* mutations.
- Immunotherapy is being extensively studied in the preoperative and postoperative settings.
- Novel clinical trial designs are needed to accelerate advances in the treatment of patients with curable NSCLC.

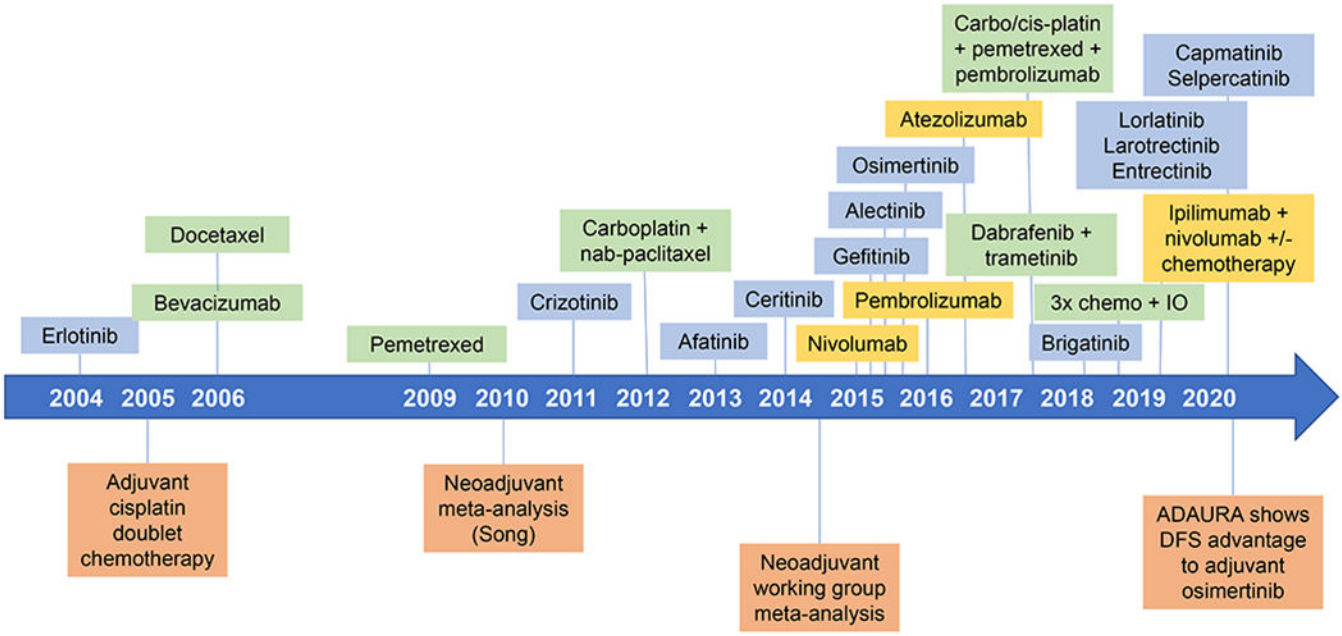

Fig. 1 |. Treatment of metastatic and non-metastatic NSCLC.

Timeline showing drugs approved or indicated for the treatment of metastatic and non-metastatic non-small cell lung cancer (NSCLC) as of December 2020. When several approvals were made in a year, they are arranged chronologically from top to bottom.

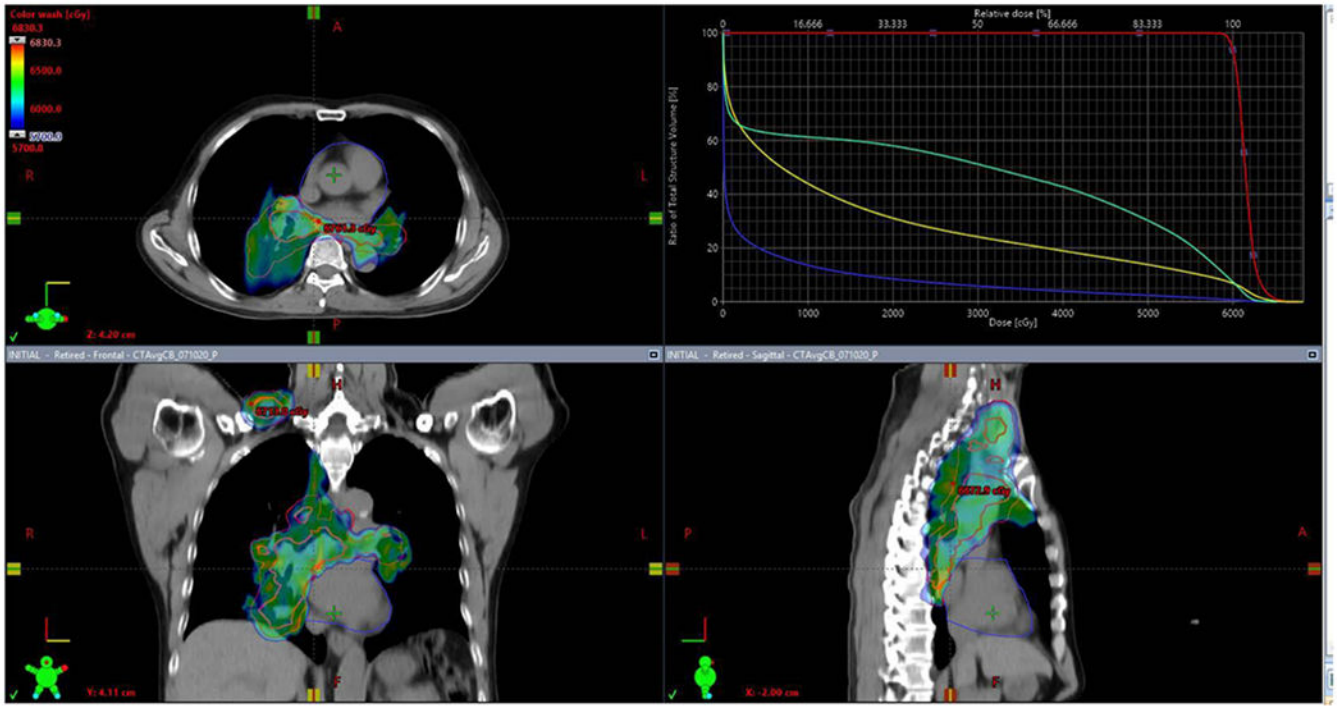

Fig. 2 |. Graphic depiction of a definitive proton radiotherapy dose distribution in a patient with stage IIIC non-small cell lung cancer (NSCLC).

On the axial (upper left), coronal (lower left) and sagittal (lower right) views of the radiotherapy plan, the red target delineation represents the gross tumour volume extending from the primary tumour in the medial right lower lobe to the bilateral hilar areas, mediastinum and right supraclavicular fossa. The dose–volume histogram (upper right) represents the radiation dose delivered to each structure of interest; it demonstrates that the gross tumour volume (red) receives close to 100% of the intended radiation dose with a steep dose fall-off to the oesophagus (green), bilateral lungs combined (yellow) and the heart (blue). Courtesy of Dr A.F. Shepherd, Memorial Sloan Kettering Cancer Center, New York, USA.

Table 1 |

Ongoing phase III studies of adjuvant therapy in non-metastatic non-small cell lung cancer.

Drug	Comparator group	*n*	Biomarker tested	Biomarker selected	Chemotherapy	End point	Refs
Crizotinib	Observation	168	*ALK* fusion	Yes	SOC	OS	NCT02201992 (REF.[132])
Erlotinib	Observation	450	*EGFR* mutation	Yes	SOC	OS	NCT02193282 (REF.[133])
Osimertinib	Placebo	688	*EGFR* mutation	Yes	SOC	DFS	NCT02511106 (REF.[62])
Nivolumab	Observation	905	PD-L1 positivity	No	SOC	DFS and OS in all patients DFS in patients with high PD-L1 (≥50% staining)	NCT02595944 (REF.[134])
Pembrolizumab	Placebo	1,177	PD-L1 positivity	No	SOC	DFS	NCT02504372 (REF.[135])
Atezolizumab	Observation	1,280	PD-L1 positivity	No	Cisplatin doublet	DFS in all patients (including PD-L1 subgroup)[a]	NCT02486718 (REF.[136])
Durvalumab	Placebo	1,360	PD-L1 positivity	No	SOC	DFS in patients with PD-L1 ≥25% in tumour cells	NCT02273375 (REF.[137])
Durvalumab	Placebo	332	ctDNA	Yes	Platinum doublet	DFS	NCT04385368 (REF.[129])
Canakinumab	Placebo	1,500	None	No	SOC	DFS	NCT03447769 (REF.[138])

[a]Further details not provided.

ctDNA, circulating tumour DNA; DFS, disease-free survival; OS, overall survival; PD-L1, programmed death ligand 1; SOC, standard of care.

Table 2 |

Ongoing phase III studies of neoadjuvant therapy in non-metastatic non-small cell lung cancer.

Neoadjuvant	Control	*n*	Adjuvant	End points	Biomarker	Refs
Platinum doublet + durvalumab	Platinum doublet + placebo	800	Durvalumab versus placebo	MPR EFS	PD-L1 positivity	NCT03800134 (REF.[139])
Platinum doublet + atezolizumab	Platinum doublet + placebo	450	Atezolizumab versus placebo	EFS MPR	PD-L1 positivity	NCT03456063 (REF.[140])
Cisplatin doublet + pembrolizumab	Cisplatin doublet + placebo	786	Pembrolizumab versus placebo	EFS OS	PD-L1 positivity	NCT03425643 (REF.[141])
Ipilimumab + nivolumab or chemotherapy + nivolumab	Chemotherapy	350	None	EFS pCR	PD-L1 positivity	NCT02998528 (REF.[142])
Osimertinib or osimertinib + chemotherapy	Chemotherapy	351	Not specified	MPR	*EGFR* mutation	NCT04351555 (REF.[108])

EFS, event-free survival; MPR, major pathologic response; pCR, pathologic complete response; OS, overall survival.