REVIEW ARTICLE

Current Status and Future Perspectives on Neoadjuvant Therapy in Lung Cancer

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ABSTRACT

This Review Article provides a multi-stakeholder view on the current status of neoadjuvant therapy in lung cancer. Given the success of oncogene-targeted therapy and immunotherapy for patients with advanced lung cancer, there is a renewed interest in studying these agents in earlier disease settings with the opportunity to have an even greater impact on patient outcomes. There are unique opportunities and challenges with the neoadjuvant approach to drug development. To achieve more rapid knowledge turns, study designs, endpoints, and definitions of pathologic response should be standardized and harmonized. Continued dialogue with all stakeholders will be critical to design and test novel induction strategies, which could expedite drug development for patients with early lung cancer who are at high risk for metastatic recurrence.

Keywords: Neoadjuvant therapy; Induction chemotherapy; Resectable lung cancer; Pathologic response; Preoperative therapy

Introduction

In patients with early-stage lung cancer who are resected with curative intent, the 5-year survival rates are approximately 50% with relapses in distant sites accounting for most failures. Even completely resected primary tumors less than 1 cm in size without evidence of nodal spread carry a suboptimal prognosis, with 8% of patients dying from their disease within 5 years and more than 25% of patients with stage I recurring within

5 years.[1-3] Patients with breast cancer routinely receive additional therapies to prevent recurrence with this level of risk.[4,5] Since metastatic lung cancers are incurable, strategies to improve outcomes in patients with lung cancer that can be completely resected must eradicate or prevent metastatic spread.

Neoadjuvant chemotherapy is an accepted practice in patients with operable and locally advanced lung cancer, but the role of neoadjuvant targeted or immunotherapies is not defined. On March 1–2, 2018, the U.S. Food and Drug Administration (FDA) and the International Association for the Study of Lung Cancer (IASLC) convened a workshop of multidisciplinary experts with experience in conducting neoadjuvant trials. The goals of the workshop were to discuss the advantages and challenges of neoadjuvant strategies, to review the prior neoadjuvant experience in lung cancer, to discuss the lessons the lung cancer community can learn from neoadjuvant efforts in other cancers, to outline standards for the pathologic evaluation of resection specimens, to discuss if pathologic response can predict long-term outcomes, and to discuss new modalities to assess therapeutic response. With the emergence of immune checkpoint blockade and oncogene-targeted therapies for locally advanced and metastatic lung cancer, and with signals of activity in the neoadjuvant setting, the design and conduct of preoperative trials has become increasingly relevant. The group concluded that it is critical to harmonize eligibility, response assessment, and efficacy outcomes for neoadjuvant studies. Trials must provide the data necessary to test whether pathologic response can predict survival. Early engagement with regulatory agencies will be essential to evaluate whether neoadjuvant trials can serve as the basis for accelerated or conditional approvals. The neoadjuvant approach provides unique opportunities to enhance curability, to shorten timelines necessary to demonstrate the benefit of perioperative therapies, and to accelerate the development of new agents for lung cancer.

Neoadjuvant Therapy in Other Tumor Types

Lung cancer trialists can take advantage of lessons learned from other cancers where neoadjuvant clinical trials have been conducted routinely over many decades. Neoadjuvant trials in patients with breast cancer have shown that outcomes from chemotherapy administered before or after surgical resection produced similar overall survival (OS) and event-free survival (EFS).[6,7] A recent meta-analysis of trials in breast cancer confirmed a robust prognostic association between pathologic complete response (pCR) and EFS and OS at an individual patient level, although not at a trial level.[8]

Neoadjuvant chemotherapy in bone osteosarcomas of bone has been standard for decades, allowing response-based treatment modifications and time to plan for limb-sparing surgery.[9,10] Here, artificial intelligence has been used to quantitate the degree of necrosis to assess clinical correlations over standard methods in estimating treatment response.[11]

Neoadjuvant Therapies for Lung Cancer

Following the demonstration that neoadjuvant chemotherapy improved outcomes in patients with osteosarcomas and metastatic testicular cancer, the thoracic oncology community first tested this strategy in patients with locally advanced lung cancer, mainly in individuals with evidence of spread to mediastinal lymph nodes. Refinements in surgical techniques and perioperative care, the identification of cisplatin-based regimens that could reliably induce responses, and advances in oncologic supportive care made it possible to explore neoadjuvant approaches in case series and randomized studies. Pioneering reports by Hilaris et al.[12] and Faber et al.[13] have shown the feasibility of multimodality therapy, that complete resections were achieved in a majority of patients, response and occasionally complete responses to chemotherapy were common in resection specimens, and that outcomes appeared improved over surgery alone. Randomized trials led by Rosell et al.[14], Roth et al.[15], Pisters et al.[16], Felip et al.[17], and Scagliotti et al.[18] comparing neoadjuvant chemotherapy before surgery to surgery alone have shown survival improvements for combined modality approaches.

Advantages of Neoadjuvant Therapy

Factors favoring neoadjuvant therapy are listed in Table 1. Neoadjuvant therapies attack metastases — the greatest danger to patients — at the earliest time. Changes in primary tumors provide a reliable way to assess the impact of neoadjuvant treatment on an individual's tumor and presents an opportunity to change the induction regimen before surgery.[19]

Neoadjuvant approaches can more rapidly translate clinical research findings to early drug approvals. The use of pCR for accelerated approval of HER2-targeted therapy for breast cancer shows that the neoadjuvant setting has the potential to expedite the development of new therapies.[20] Resection specimens also provide access to "persister cells" that were not eradicated by the neoadjuvant therapy and to the surrounding microenvironment that may play a role in persistence.

Clinical studies and retrospective reviews of cisplatin-based neoadjuvant regimens in lung cancer indicate better tolerability than adjuvant approaches. Compliance with subsequent therapies is also improved.

Table 1. Factors Favoring Neoadjuvant Therapy

Potential to attack micrometastases at earliest time
Ability to assess sensitivity and resistance of agents used in current adjuvant and neoadjuvant trials to inform the development of future rational combinations and the potential to change the regimen following surgery in future trials.
Pathologic response in diseases such as breast cancer may be a potential predictor of long-term outcomes. Accelerated approval may be granted if surrogate endpoints are reasonably likely to predict benefit. Longer-term endpoints (EFS, OS) could be assessed for traditional approval in the same trial or in a separate trial.
Shorter trial timelines (for assessment of a pathologic response endpoint) than adjuvant trials.
Potentially improved systemic therapy drug delivery and tolerability.
Provides an opportunity to implement preoperative smoking cessation and pulmonary "pre-habilitation" strategies.
Potentially improved compliance with subsequent therapies.
Allows for more time to identify unsuspected metastases, comorbidities, and pursue smoking cessation strategies before local therapy.

EFS, event-free survival; OS, overall survival.

The neoadjuvant therapy interval can provide additional time to implement and maintain smoking cessation preoperatively, an intervention critical to minimizing operative risk and permit pulmonary "prehabilitation" strategies.[21] In addition, neoadjuvant therapy can serve as a useful window to identify undetected metastases, sparing some patients futile surgery. The neoadjuvant therapy phase can also be an opportunity to uncover additional comorbid conditions whose management can lead to safer surgery or, if not remediable, permit efficient planning of nonoperative therapies.

The timeline for conducting adjuvant trials is so long that the approaches under study can become irrelevant. For example, ECOG 1505, studying adjuvant bevacizumab, was conceived years before study approval by the National Cancer Institute in 2005. The manuscript reporting this trial was published in 2017.[22] In breast cancer, neoadjuvant trials that use pathologic response as an early outcome measure have reported results in half the time.[23]

Surgical Considerations of Neoadjuvant Therapy

There is no evidence that the use of neoadjuvant therapy leads to less extensive surgeries or permits resection in patients deemed unresectable at diagnosis. One study evaluated possible harm from delayed surgery in early-stage lung cancer.[16] Patients not proceeding to surgery or undergoing incomplete resections were uniformly found to have comorbid conditions rendering them inoperable, or an unappreciated metastasis making surgery futile. Adding modalities to surgery increases toxicities of the entire treatment program; but in general, few unanticipated events occur, and the collective trial experience has indicated that additional toxicities can be managed, and overall risk is not excessive for treatments with the potential to cure. Because resection rates for patients with early-stage lung cancer are high and local failure rates are low, proving additional benefit in these areas is difficult and requires large sample sizes to show important differences.

Few criteria exist to select drugs for neoadjuvant use. In general, only drugs that show effectiveness and manageable toxicities in patients with stage IV disease are "brought forward" for adjuvant and neoadjuvant use. Some information on additional toxicities occurring in the perioperative setting is obtained by observing outcomes in patients with advanced disease who undergo surgeries for oligometastases or metastatic complications such as gastrointestinal obstruction.

Neoadjuvant Chemotherapy

Meta-analyses of randomized trials of neoadjuvant chemotherapy showed a significant survival advantage over surgery alone with a hazard ratio of 0.8 that equated to a survival advantage of 5% at 5 years.[24] This magnitude of survival advantage was equivalent to that provided by post-operative adjuvant chemotherapy. There is no consensus on whether, in the absence of dose-limiting toxicities, a "fixed number" of preoperative chemotherapy cycles should be administered or whether patients should be treated to best response. If a fixed number of cycles is chosen, the current norm is to use the length of treatment for the same regimen when employed in the adjuvant setting, usually 4 cycles. Although cisplatin-based regimens have been most extensively studied and serve as the standard, no consensus exists on the best drugs to combine with cisplatin. There are no data to show that the use of regimens substituting carboplatin for cisplatin is equivalent in terms of efficacy or toxicity.

Neoadjuvant Radiation Therapy

Neoadjuvant radiation therapy alone, even when it leads to pathologic response in the resection specimen, has not been shown to improve resectability or survival.[25,26] The goal of preoperative radiotherapy is to improve OS by decreasing local tumor recurrences. Decreasing local recurrence may be the primary aim in and of itself in cases where local failure impacts quality

of life, such as Pancoast syndrome.[27] Preoperative radiotherapy is more likely to have a role in stage III disease given the good local control in patients with stage I and II resected tumors.[28] The rationale to add a second local approach (and a third modality) to a regimen when one definitive local therapy is planned is unclear. Two series have shown that the addition of radiotherapy to chemotherapy did not improve survival over chemotherapy alone, even when pCR rates were higher.[29,30] There is the suggestion that rates of incomplete resection may be decreased in selected patients following chemoradiotherapy, comparable to the earlier experience in superior sulcus tumors.[29,31]

Immune Checkpoint Blockade

In stage IV lung cancer, immune checkpoint inhibitors including anti–programmed death 1 and programmed death ligand 1 antibodies alone, or combined with chemotherapy, prolonged survival. Early experiences with neoadjuvant nivolumab (n = 21) and atezolizumab (n = 21) reported a rate of major pathologic response (MPR) ranging from 21% to 45%, acceptable toxicity, and no increase in operative mortality.[32-35] In the trial studying neoadjuvant nivolumab, 20 of 21 (95%) patients underwent complete resections.[34] It is possible that immune checkpoint blockers may best be used via a neoadjuvant approach where the immune landscape of the primary tumor and draining lymph nodes remains intact. In pre-clinical models in breast cancer, there is improved efficacy of neoadjuvant immunotherapies compared to adjuvant.[36]

Combined Chemotherapy and Immune Checkpoint Blockade

Initial experiences in small numbers of patients with neoadjuvant chemotherapy and immune checkpoint inhibitors (n = 14) suggested activity and acceptable toxicity, without new or enhanced operative complications.[37] Questions remain as to the choice of chemotherapy and if there is a rationale to use modalities concurrently or sequentially. Randomized trials studying neoadjuvant chemotherapies alone and with immune checkpoint blockers are underway (Supplemental Table 1).

Oncogene-Targeted Therapies in Patients With Lung Cancer

Targeted molecular therapies produce response rates that reliably exceed 50% with decreased toxicities compared to cytotoxic chemotherapies.[38] In one study, adjuvant gefitinib was better tolerated and had superior disease-free survival (DFS) compared with adjuvant cisplatin-based chemotherapy in patients with resected *EGFR*-mutant tumors.[39] This trial and other series have sparked great interest in using targeted therapies in the neoadjuvant setting. Case studies have shown that this approach is feasible and that resecting tumors in patients receiving *EGFR* and *ALK* kinase inhibitors identifies no new toxicities and no greater incidence of perioperative complications.[40] Unlike the situation in patients with advanced lung cancer where "upfront" genotyping to detect oncogenic drivers is a standard of care, for patients with early-stage lung cancer, the guidelines defer routine genotyping at diagnosis to the discretion of the institution.[41] The situation is further complicated by days to weeks of waiting time for tissue genotyping results. The availability of rapid immunohistochemistry tests on routine diagnostic specimens and genotyping of circulating tumor DNA (ctDNA) from blood shorten timelines; however, the sensitivity of ctDNA testing may be reduced in early-stage disease.[42] The optimal duration of targeted neoadjuvant treatment and the length of post-operative use are unknown. Most propose 8 weeks of targeted therapy preoperatively and 2 or 3 years of treatment postoperatively after stage-appropriate adjuvant chemotherapy and radiation are completed. Neoadjuvant use of targeted therapies provides a singular opportunity to collect and study "persisters," those tumor cells that remain and may predict recurrence despite targeted therapies. The Lung Cancer Mutation Consortium has proposed the PROMISE umbrella trial (Fig. 1) to test for the presence of oncogenic drivers at diagnosis in patients with resectable stage I-III lung cancer and to use that information to recommend matched targeted therapies before resection.[43,44]

Imaging Techniques to Assess Neoadjuvant Response

Computed Tomography

Computed tomography (CT) is a commonly used imaging technique for measuring objective cancer response to systemic therapy using selected target lesions as a reflection of disease response. The most commonly used criterion used in clinical research is unidimensional measurement per Response Evaluation Criteria in Solid Tumors.[45] Bidimensional WHO criteria are also used. Despite the advantages of available, quick, and reproducible technology, the usefulness of standard CT measurements to assess response to neoadjuvant therapy is limited. Although the objective CT response rate with neoadjuvant platinum-doublet chemotherapy is generally higher in the early-stage setting than in the treatment of metastatic disease, the absolute survival advantage at 5 years is 5%.[46] CT response by Response Evaluation Criteria in Solid Tumors also did not correlate with pathologic response in a retrospective study.[17,47,48]

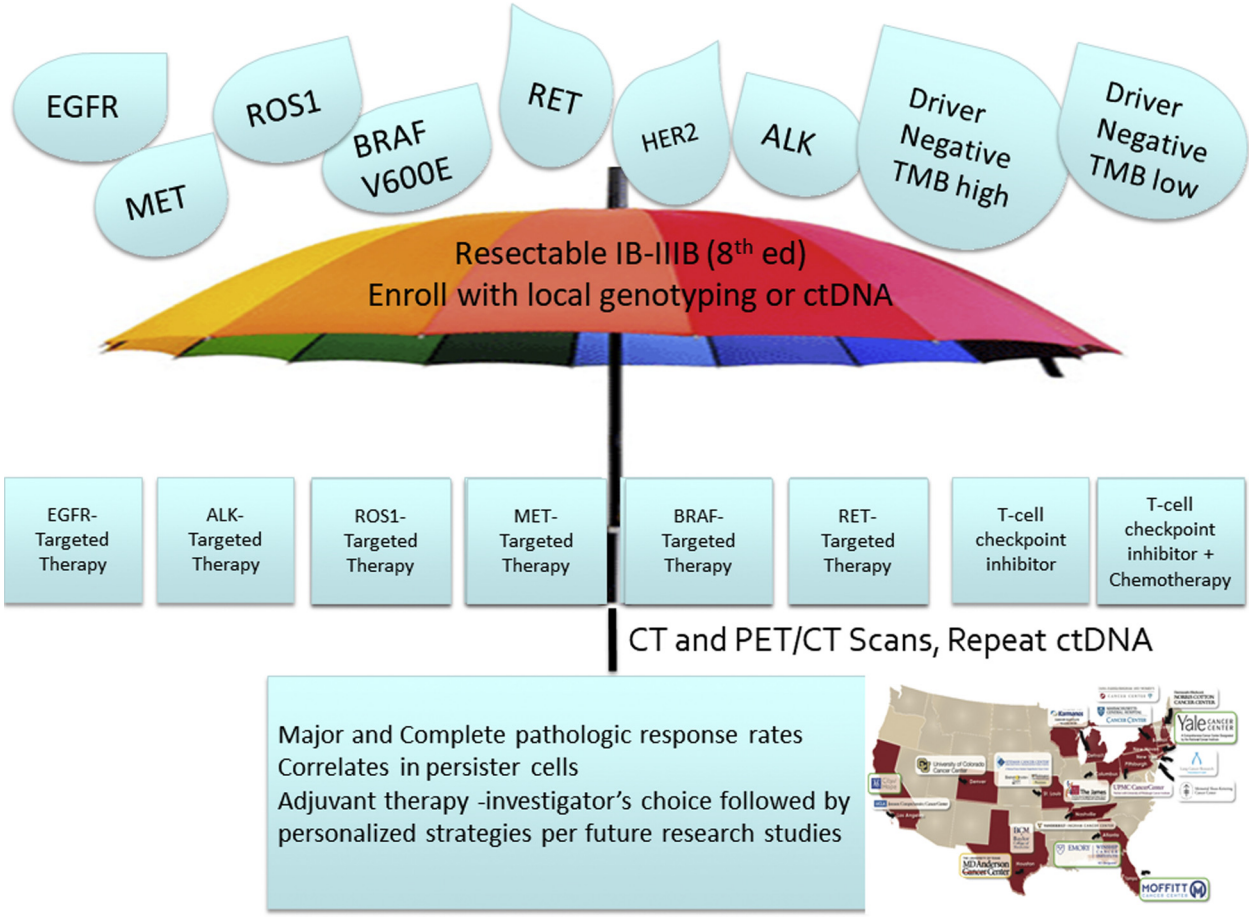

Figure 1. LCMC4 PROMISE. Schema of the proposed trial of the Lung Cancer Mutation Consortium (LCMC) to identify oncogenic drivers at diagnosis and to match targeted neoadjuvant therapies to the drivers detected in patients with early stage lung cancer. CT, computed tomography; PET, positron-emission tomography; ctDNA, circulating tumor DNA.

This discrepancy may be more pronounced when evaluating response to neoadjuvant immunotherapy.[34]

Positron-Emission Tomography Scan

Before surgery and consideration of neoadjuvant therapy, staging with brain magnetic resonance imaging and 18F-fluorodeoxyglucose positron-emission tomography (PET) scan are recommended.[49] The standard uptake value (SUV) or metabolic activity of primary tumors and lymph nodes have been considered for response assessment in advanced disease by the Positron-Emission Tomography Response Criteria in Solid Tumors criteria.[50] Percent change in SUV was a better predictor of outcome after neoadjuvant therapy than the radiographic change in size of the same lesions.[48,51,52] Pre- and post-treatment PET scans have been analyzed from neoadjuvant trials, with proposals of percent remaining and percent change as potential predictive or prognostic biomarkers.[53-56] A PET adaptive study has been performed, assigning switch therapy in patients who do not respond by a predefined SUV criterion.[19] Whereas PET response to neoadjuvant therapy may be associated with improved outcomes, no definition of PET response has been universally adopted. As these functional imaging studies are performed pre- and post-therapy as part of routine care and in research protocols, efforts should be made to uniformly collect and analyze this data.

Pathologic Response Assessment

The occurrence of pCR with cisplatin-based chemotherapy is generally less than 10%, thus it is impractical to use pCR as a primary endpoint for neoadjuvant chemotherapy trials. Pathologic nodal downstaging has been proposed as a predictor of efficacy, although it can only be applied to those with biopsy-proven pre-treatment nodal disease and to date has not been associated with improved survival.[51]

Many studies have identified a major response criterion of 10% or less residual tumor cells (MPR) as a pathologic correlate of improved long-term outcomes.[29,48,57-59] This has led to use of MPR as one

endpoint to characterize the activity of neoadjuvant chemotherapy.[60]

With the increasing use of pathologic response in trials, the pathologic assessment of resected lung cancer following neoadjuvant therapy is of growing importance. In 2017, the College of American Pathologists published a template for assessing specimens that includes the percent residual viable tumor. This was also endorsed in the United Kingdom. Using the experience of high volume academic centers, the thoracic pathology community, including the IASLC Pathology Committee, has committed to defining and standardizing the pathologic assessment of resection specimens following neoadjuvant therapy.

Standardization of Pathologic Assessment

Reporting standards were proposed, although a standardization of methodology to process and examine these resection specimens is not fully defined. Many have used the systematic sampling with serial sections through a resected tumor followed by averaging as originally proposed by Pataer et al.[59] and modified by Hellmann et al.[60] (Fig. 2). MPR determined by this methodology may predict long-term outcomes, and once standardized it could be incorporated into current protocols.

The items requiring future definition include 1) tumor "grossing," including radiographic-pathologic correlation to identify and measure the size of the tumor bed; 2) systematic sampling through the tumor bed including the border with surrounding lung to define the edge of the tumor bed; 3) estimation of percent viable tumor per slide with adjustment for varying amounts of total material on different slides and tissue not sampled due to grossly identified necrosis and cavitation; 4) inclusion of treatment response or viable tumor cells in regional lymph nodes, an element not present in the current MPR definition; and 5) assessment of pathologic response of multiple primary tumor nodules.

A comprehensive assessment of the resection specimen cannot be achieved without coordination and communication from the medical oncologist, relaying the preoperative treatment to the thoracic oncologic surgeon, the staff in the pathology gross lab, and ultimately to the pathologist performing the assessment. A standardized and thorough pathologic response assessment protocol will be a powerful tool for data collection going forward.

Additional Considerations for Pathologic Assessment for Patients Receiving Immunotherapeutics

Current pathologic response criteria were developed studying tumors following cisplatin-based chemotherapy, with responses largely induced by cytotoxic cell death (necrosis and fibrosis). The commonly used methods of MPR assessment serially section the "tumor," but do not specify an examination of what was once

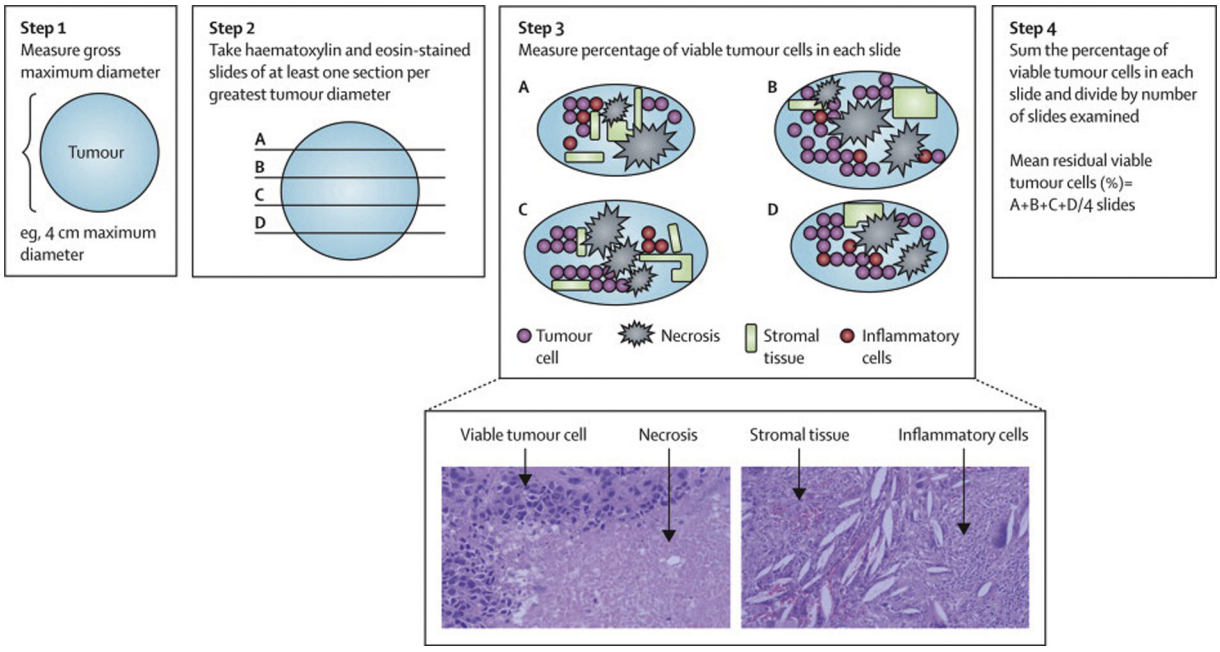

Figure 2. Method for assessment of percentage of viable residual tumor in resection specimens following neoadjuvant therapy.[59,60]

tumor and is now tumor regression bed. Given the different mechanisms of action of chemotherapeutic, oncogene-targeted, and immunotherapeutic agents, distinct features may be observed in the regression bed which could provide biologic insights and additional predictive and prognostic information.

In evaluating the resection specimens in a cohort of 20 patients treated with neoadjuvant nivolumab, the two extremes of the group were compared — nine patients with 10% or less residual viable tumor, and four with more than 90% residual tumor volume.[34] The pathologic features of the regression bed included proliferative/new fibrosis, neovascularization, dense tumor infiltrating lymphocytes, the formation of tertiary lymphoid structures, cholesterol clefts with giant cells, and plasma cells, although not every feature is present in each case.[61] Because the regression bed is near but not part of the residual tumor, these areas must be specifically collected and processed at the time of gross examination. Radiographic correlation may aid in identification of the regression bed.

Based on the observations above, Cottrell et al.[61] have proposed modifying pathologic response criteria to add the area of the regression bed to the areas of residual viable tumor and necrosis. In addition, the terms "stroma," "fibrosis," and "inflammation" are more specifically detailed to include only proliferative fibrosis (versus old, hyalinized fibrosis or any fibrosis), dense (versus mild) tumor infiltrating lymphocytes, and tertiary lymphoid structures (versus non-organized lymphoid aggregates).

Today, similar criteria to determine percent necrosis following neoadjuvant therapy can be used with both chemotherapy and immunotherapy. Pathologic response assessment following chemotherapy routinely evaluates the entire lung to identify the tumor regression bed. A detailed evaluation of the post-therapy regression bed can be undertaken and included in the overall assessment of response after neoadjuvant therapies. The pathology research community is in the process of standardizing techniques and definitions of response in resection specimens, building on the current descriptions of methodology.

Molecular Pathologic Considerations for Neoadjuvant Trials

The College of American Pathologists, the IASLC, and the Association of Molecular Pathology have issued guidelines for the molecular testing of biopsy specimens from patients with advanced lung cancer.[62] These guidelines require a turnaround time of 10 days from sample receipt to reporting of all results. This turnaround time does not account for the time from biopsy suite to pathology accessioning, pathologist sign-out, and transfer to the molecular laboratory. Furthermore, the date of specimen arrival to the lab may impact turnaround time, based on how each individual laboratory manages batching of assays. These practical issues are of extreme importance in neoadjuvant therapy trials, a setting in which a delay in awaiting results is perceived as a delay in curative surgery. Laboratories must use highly targeted, but rapid assays in combination with next-generation sequencing.

Liquid Biopsy Specimens

Liquid biopsy specimens analyzing ctDNA represent a promising approach for monitoring responses during and after neoadjuvant therapy. Although a majority of prior liquid biopsy studies have studied patients with advanced-stage disease, several have focused on earlier stages.[63] These have revealed that between 15% and 50% of patients with stages I through III have detectable circulating tumor cells in the peripheral blood at diagnosis.[64-68] By comparison, ctDNA appears to be present in 50% to 95% of patients with stages I through III, suggesting it may be a more broadly applicable biomarker in this setting.[63,69,70] These sensitivities were achieved using research assays and not clinically available tests developed for assessment of patients with advanced lung cancer. Although no studies have explored ctDNA response assessment during neoadjuvant therapy in lung cancer, a recent study in rectal cancer provides proof of concept that ctDNA changes after neoadjuvant therapy and before surgery may be prognostic.[71]

Intriguingly, studies suggest that residual ctDNA after curative-intent surgery or radiotherapy of localized lung cancer is a sensitive and specific marker of patients at highest risk of recurrence. Minimal residual disease can be detected shortly after treatment and ctDNA changes during adjuvant chemotherapy may be predictive of outcome.[63,69] Thus, liquid biopsy is a promising tool for noninvasively monitoring response to treatment. To explore the clinical utility of these assays in patients receiving neoadjuvant therapy, future trials should include serial sample collection for liquid biopsy specimens and examine questions such as the ability of these tests to predict treatment response early during neoadjuvant therapy, correlation with MPR and pCR, and ability to identify patients who may benefit from additional treatment after surgery.

Neoadjuvant Trials: An Industry Perspective

Neoadjuvant therapy may be better suited than adjuvant therapy for evaluating new agents, as the effect

of the drug on the target can be assessed by pretreatment biopsy and after treatment at surgery.

There is a high level of interest in the pharmaceutical industry to evaluate new agents, particularly immunotherapeutics, in the neoadjuvant setting in early-stage lung cancer based on unmet need, strong biological rationale, and early reports of activity and safety. Several industry-sponsored and supported phase 1 and 2 studies are evaluating immunotherapies as single agents or in combination with chemotherapy or radiotherapy. Recently, three phase 3 randomized trials have been initiated evaluating neoadjuvant programmed death 1/programmed death ligand 1 inhibitors in combination with chemotherapy or anti–CTLA-4 in lung cancer (Supplemental Table 1). Evidence for neoadjuvant targeted treatment is limited and no phase 3 studies have been performed in patients with *EGFR*-mutant lung cancer. Phase 2 neoadjuvant trials of crizotinib for patients with early-stage lung cancer with *ALK* or *ROS1* fusions or MNNG HOS transforming gene (*MET)* mutations and osimertinib for patients in whom *EGFR* mutations are ongoing.

Supplemental Table 2 lists clinical design and implementation considerations unique to neoadjuvant trials in lung cancer that have arisen in the course of initiating the ongoing immunotherapeutic and targeted therapy studies (Supplemental Tables 3 and 4).

Regulatory Considerations for Neoadjuvant Drug Development

Biomarkers intended to be surrogate endpoints should capture the effects of a therapy on long-term outcomes. To be a robust surrogate, these biomarkers should lie in the causal pathway of the disease process. Accelerated approval provisions allow the FDA to grant accelerated approval to a drug for a serious or life-threating disease when it has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than the development of irreversible morbidity or mortality, considering the severity, rarity, or prevalence of the condition, and the availability or lack of alternative treatments.[72] The FDA may grant traditional approval if a drug shows a direct clinical benefit or based on an improvement in an established surrogate. An established surrogate differs from a "reasonably likely" surrogate in that an established surrogate can be used to support traditional approval.

An established surrogate should meet the Prentice criteria or modified criteria that can provide evidence from randomized controlled studies to replace a clinical benefit endpoint with the validated surrogate endpoint for traditional approval.[73] The surrogate endpoint should be correlated with the clinical outcome, and should capture the complete net effect of the treatment on the clinical outcome. To establish a surrogate endpoint, both individual patient-level correlation and a trial-level correlation should be met.

When a new endpoint such as pCR or MPR is being considered for accelerated approval, adequate data should support that the surrogate endpoint is a prognostic marker at the individual-level (e.g., responders have better outcomes than nonresponders), and data should indicate that the magnitude of difference in pathologic response rate between treatment arms is likely to predict long-term benefit. Pathologic responses with immunotherapy may impact EFS or OS differently than pathologic responses with chemotherapy or targeted therapy. The FDA has accepted DFS or EFS as a traditional approval endpoint for adjuvant indications in melanomas, renal cell carcinomas, breast cancer, gastrointestinal stromal tumors, and colorectal cancer, either because these are established surrogates or are indicative of direct clinical benefit, as a delay in the emergence of metastatic disease is clinically meaningful.

The 2012 Draft Guidance for Industry describing the pathway to use pCR for accelerated approval in early breast cancer was finalized in 2014.[74] The FDA investigated pCR as an endpoint to support drug approval, forming the CTneoBC working group with other stakeholders.[8] Pertuzumab was granted accelerated approval in neoadjuvant *Her2*+ breast cancer in 2013 and regular approval in 2017.[75] Pertuzumab had previously been approved for the treatment of patients with metastatic breast cancer based on a large survival effect when added to trastuzumab and docetaxel, and the established safety and efficacy of pertuzumab in the metastatic setting added to the totality of evidence to support the neoadjuvant approval.[76] For lung cancer, available data is consistently supportive but today is insufficient to prove whether MPR or pCR predicts EFS and OS. This topic was reviewed by Hellmann et al.[60] in 2014. In 15 trials of neoadjuvant chemotherapy, the median rate of pCR was 4% (range, 0% to 16%). An early series by Pisters et al.[77] reported a 54% 5-year survival for patients with stage IIIA disease with pCR after neoadjuvant chemotherapy. Reports by Betticher et al.[51], Depierre et al.[47], Pataer et al.[59], Chaft et al.[57], and Mouillet[78] indicate that pCR following chemotherapy predicts survival at the individual level.

An advantage of the neoadjuvant approach is that this strategy enables switching to different, potentially more effective therapies post-surgically.[79] An informal query of recent European Medicines Agency experience through the scientific advice process specifically related to neoadjuvant approaches in lung cancer suggested that proper studies describing the potential discordance between the response in the primary tumor versus the local-regional lymph nodes should be explored, and

histopathologic analyses will be required. In addition, because MPR has not been established as a surrogate endpoint, further study of the association between MPR and longer-term outcomes in various histologies and genetic subgroups and pharmacologic classes of neoadjuvant therapies should be explored.

Challenges to Accrual to Neoadjuvant Studies

Virtually all phase 3 and many phase 2 adjuvant and neoadjuvant trials in lung cancer have struggled to meet accrual goals and as a consequence, the literature is replete with underpowered studies.[80,81] Some of the reasons for low accrual include a smaller patient pool than in the metastatic setting, concern over using therapies with only small predicted benefits that delay definitive therapy, and a small number of surgeons willing to perform these trials and resections after neoadjuvant therapies. Furthermore, patients with resectable lung cancer differ markedly from individuals with breast cancer as they are older, have more tobacco-related comorbidities, and the surgery is more complex.[82]

To overcome these obstacles, thoracic surgical oncologists must have a central role in trial design and safety and data review. The global reach of industry-sponsored neoadjuvant trials can enhance accrual. Ensuring the quality and consistency of surgical procedures will be critical to success. Furthermore, research study coordinators specifically trained to conduct neoadjuvant studies are essential. While the study is ongoing, consistent and collaborative tracking of patients is critical. To attract surgeons to these trials, it is important to study new technologies and therapies, have repeated surgical meeting presentations and publications, and structure the study and data analysis to allow for "stand-alone" surgically focused publications. Because neoadjuvant trials include patients who may be cured by surgery alone, clearly addressing safety concerns is critical.

Conclusions

Neoadjuvant chemotherapy in early-stage lung cancer improves EFS and OS to the same extent as adjuvant chemotherapy. Today, health authorities need additional data to determine whether pathologic response criteria such as MPR or pCR can serve as a surrogate endpoint (a

Table 2. Summary of Neoadjuvant Study Design Considerations

All patients with lung cancer are at risk for recurrence following complete surgical resections. The risk increases with stage.
The most frequent and concerning form of recurrence after complete resection is metastasis. Therapies to prevent recurrence must address the threat of metastasis.
Cisplatin-based chemotherapy administered either before or after surgery improves survival.
Cisplatin-based chemotherapy administered before surgery does not enhance resectability or permit lesser resections.
Radiation combined with cisplatin-based chemotherapy likely does not enhance resection rates or survival beyond chemotherapy alone and adds toxicity.
Radiation combined with cisplatin-based chemotherapy may provide benefits based on stage and the location of the tumor.
Immune checkpoint blockade and oncogene-targeted drugs are appropriate for investigation as neoadjuvant therapies because of their established efficacy and safety in the metastatic setting, and preliminary signals of activity in earlier stages.
The experiences with neoadjuvant approaches in patients with breast cancer and osteosarcomas provide both a theoretical framework and practical information that can be readily applied to neoadjuvant trials in patients with lung cancer.
Uniform and rigorous procedures to assess pathologic response are essential. For studies with registrational intent, the ability to measure the early endpoints of MPR and pCR consistently and reliably will be critical. Professional organizations such as IASLC can assist the surgical pathology community in establishing standards.
Studies should document cigarette smoking status in all patients and implement a smoking cessation program for current smokers.
Neoadjuvant trials should report standard outcomes: complete resection rate, MPR, pCR, rates of pathologic downstaging, DFS/EFS, OS, % survival at 1, 2, 3, 4, and 5 years, sites of first recurrence, accepted reporting of surgical complications (length of stay, rehospitalization, and 30- and 90- day mortality).
Perioperative collection and storage of blood, high resolution CT and PET/CT images, and digital pathologic images are important for studying emerging technologies using artificial intelligence.
Assess sensitivity and resistance of agents to define mechanisms of persistence as part of drug development and research.
Document precise clinical and pathological staging for each patient using the eighth edition of TNM for lung cancer.[83]
Create uniform eligibility criteria; operability, and resectability based on a multidisciplinary evaluation.
Consistent imaging: Pre-treatment and pre-operative chest CTs (with intravenous contrast), pre-treatment and pre-operative PET-CT.
Standardize follow-up testing and evaluation intervals consistent with guidelines for patients with complete resections: Surveillance visits every 6 months for 3 years, then yearly. Interval history, physical examination, smoking cessation, chest CT with contrast every 6 months for 3 years, then a low-dose, noncontrast chest CT scan yearly.[41]
Continue discussions with health authorities regarding the potential for accelerated or conditional drug approvals if MPR, pCR, or other reproducible changes can predict EFS and OS.

MPR, major pathologic response; pCR, pathologic complete response; IASLC, International Association for the Study of Lung Cancer; DFS, disease-free survival; EFS, event-free survival; OS, overall survival; CT, computed tomography; PET, positron-emission tomography.

summary of neoadjuvant study design considerations can be found in Table 2). To obtain the data necessary to support surrogacy, the lung cancer community should standardize the definition of MPR and pCR and use this standard definition in all ongoing and planned neoadjuvant trials of immunotherapy, targeted therapy, and combination therapy. It will be imperative to determine the relationship of MPR and pCR to both EFS and OS in these trials, with meta-analyses (analyzing all trials as well as dividing trials by molecular and disease subtype and pharmacologic class of drug) to determine if MPR or pCR predicts survival. It will also be important to use residual tumor in surgical resection specimens to understand determinants of persistent cell survival which may inform trials investigating post-operative approaches.

Major goals of neoadjuvant trials are curing more patients, more rapid identification of agents that can improve outcomes following complete resections, and standardization of endpoints and trial design to acquire sufficient data necessary to use neoadjuvant results for expedited drug development pathways.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2018.09.017.

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