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Lung Cancer Update

from NEJM Group

- Adjuvant & Neoadjuvant Chemotherapy for Resectable NSCLC
- Antibody–Drug Conjugates
- Disparities in Care & Lung Cancer Outcomes
- Radiotherapy's Role in Early-Stage Lung Cancer

Editor
Jessica Donington, MD

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Customer Service
(800) 843-6356, or email nejmcust@mms.org.

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FROM the Editor

Treatment in thoracic oncology continues its rapid evolution. The broad integration of targeted agents and cancer immunotherapies dominate the treatment and research landscape, but advancements and research questions now extend beyond first- and second-line use in the advanced setting. Use of these agents is expanding to earlier-stage patients and investigators are asking deeper questions. This special issue addresses some of the most poignant of these questions.

A concern at the forefront for many clinicians and researchers alike are treatment options for patients who progress on immunotherapy. Antibody–drug conjugates hold incredible potential to be the next great breakthrough and treatment options for these patients. This promising technology pairs a strong cytotoxic with a cancer-specific antibody that allows the powerful agent to be delivered and activated only in malignant cells. This concept has been an oncologic dream for years, and these agents are now in clinical trials. Experts in the field review current technology and ongoing trials for these agents.

Clinicians and researchers also question the current ability to get these ground-breaking treatments to patients in an equitable manner. As the science of lung cancer evolves and treatments improve, divergent outcomes between the haves and have-nots become more pronounced. Health care inequality is complex in the United States and throughout the world. It is becoming obvious in thoracic oncology that treatment discovery is only part of the battle, and fair and equitable access is equally important, but not currently happening. Significant inequities in lung cancer care are highlighted here.

The newest use for cancer immunotherapies is in resectable disease. In the past 2 years, new evidence for benefit and FDA approvals for use of cancer immunotherapies has emerged in both the adjuvant and neoadjuvant settings. Two surgical experts and clinical trial leaders review the ongoing evidence and indications in the adjuvant and neoadjuvant settings.

We are witnessing unprecedented progress in our understanding and treatment of lung cancer, and there is no reason to think this exceptional progress will slow down, since each great discovery sets the groundwork for the next.

Jessica Donington, MD, Editor

Dr. Donington is General Thoracic Surgeon and Chief, Section of Thoracic Surgery, University of Chicago Medicine. She reports medical writing support from Roche/Genentech; speaker's bureau fees from AstraZeneca, Roche/Genentech, and Bristol Myers Squibb; and participation on an advisory board for Biodesix.

Topic Update

Antibody–Drug Conjugates for Lung Cancers

Bob T. Li, MD, PhD, MPH, Mélissa Prat, PhD, and Julien Mazières, MD, PhD

Although lung cancer mortality has substantially decreased in recent years due to advances in screening and systemic therapy, it remains the leading cause of cancer deaths. Standard systemic therapies include chemotherapy, immune checkpoint inhibitors, and oncogene-directed targeted therapies, which are components of the current armamentarium against all stages of lung cancer. Antibody–drug conjugates (ADCs) are a new class of drugs on the horizon that will potentially transform the field of thoracic oncology and provide new hope for patients with lung cancer. Here we provide a synopsis of the mechanisms of action and an update on the development of ADCs toward a new treatment paradigm for lung cancers.

Molecular Mechanism of Action

ADCs first arrived in the oncology clinic over two decades ago, with FDA approval of the anti-CD33 gemtuzumab ozogamicin for patients with acute myeloid leukemia in 2000. ADCs consist of a monoclonal antibody backbone conjugated with potent cytotoxic chemotherapy payloads via linkers; therefore, these drugs are delivered intravenously. Central to their mechanism of action is antibody binding to proteins expressed at cancer cell surface, and internalization of the receptor-ADC complex into the cancer cell with subsequent intracellular release of the cytotoxin while sparing normal cells (*Nat Rev Clin Oncol* 2021; 18:327). Through this targeted approach via ADCs, the cytotoxic chemotherapy may be safely delivered at multiple-fold higher potency, enabling greater antitumor efficacy compared with unconjugated chemotherapy. This cytotoxic mechanism may trigger activation of immune cells and antibody-dependent cellular cytotoxicity, potentially eliciting long-term immune responses (*Sci Transl Med* 2015; 7:315). Target identification and bioengineering modifications to the antibody Fc region, cytotoxic payload, drug-to-antibody ratio, linker stability, and membrane permeability have led to newer generations of ADCs subsequently approved for a growing number of cancer types including lymphomas, breast, urothelial, cervical, and gastric cancers.

Development in Lung Cancers

Clinical efforts using monoclonal antibodies in targeting EGFR, HER2, and MET protein expressions in lung cancers were historically disappointing. The anti-HER2 ADC trastuzumab emtansine also failed to produce substantial activity in an international clinical trial targeting HER2-expressing lung cancers (*Clin Cancer Res* 2019; 25:64).

The first positive clinical trial targeting *HER2*-mutant lung cancers used trastuzumab emtansine, which produced an overall response rate of 44% and median progression-free survival of 5 months (*J Clin Oncol* 2018; 36:2532). This was a surprise to the field, as *HER2* mutations did not commonly overexpress HER2 protein, and the positive trial results contradicted a traditional understanding that ADCs rely on target protein overexpression to deliver their cytotoxic payload. Translational and mechanistic research discovered that HER2 hyperactivated through gene mutations or amplification increased ubiquitination and internalization of the receptor-ADC complex for enhanced delivery of cytotoxic payload regardless of protein expression (*Cancer Discov* 2020; 10:674).

These findings validated drug development plans of multiple ADCs in targeting oncogene-driven lung cancers regardless of protein expression, including trastuzumab deruxtecan for *HER2*-mutant lung cancers and patritumab deruxtecan for *EGFR*-mutant lung cancers, both of which have achieved FDA breakthrough therapy designation (*N Engl J Med* 2022; 386:241; *Cancer Discov* 2022; 12:74). Trastuzumab deruxtecan was granted FDA priority review based on its registrational trial showing an overall response rate of 55% and a median progression-free survival of 8 months in patients with treatment-refractory, *HER2*-mutant lung cancers; therefore,

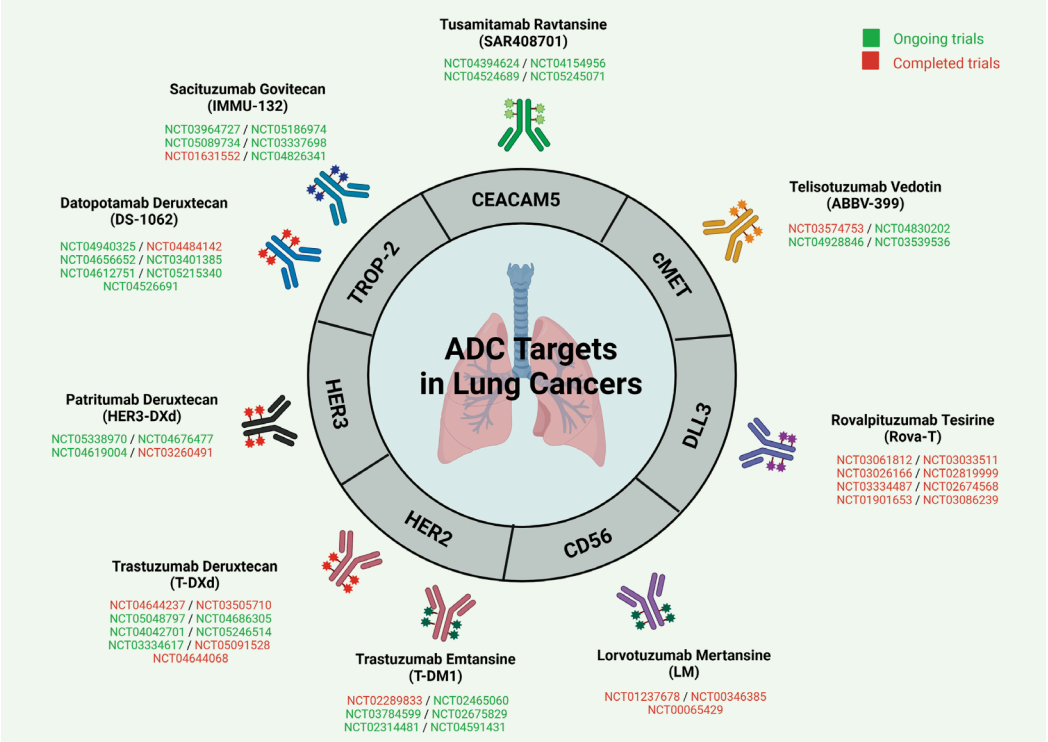
it has the potential to become the first ADC approved for patients with lung cancers. Furthermore, trastuzumab deruxtecan is currently being investigated as a potential first-line therapy in the DESTINY-Lung04 trial (NCT05048797).

Following the early successes of these ADCs, a growing number of new lung cancer targets are being explored in early-phase clinical trials of novel ADCs, including cMET, TROP-2, CEACAM5, CD56 and DLL3 (Figure). As many of these ADC trials are not biomarker selected, response rates will likely be lower, but clinical development may be feasible in the later-line settings. Biomarker research is crucial to predict patient benefit and optimize personalized medicine. Toxicities are similar to those of chemotherapy and include myelosuppression and gastrointestinal disturbance. Although cytotoxic toxicities are generally mild and manageable with the targeted delivery through ADCs, interstitial lung disease and pneumonitis are increasingly recognized as potentially serious or fatal adverse events (*JAMA Oncol* 2021; 7:1873). Management algorithms are being studied and developed for early detection and intervention to reduce the incidence and minimize complications of severe interstitial lung disease or pneumonitis (*Cancer Treat Rev* 2022; 106:102378).

Implications for the Future

ADCs have made substantial progress in their clinical trial development and are rapidly becoming a new class of drugs for lung cancers. The most promising ADCs with potential regulatory approval in the near future are directed against oncogene drivers such as *EGFR* and *HER2* mutations, whereas others

FIGURE: Antibody–Drug Conjugate Targets in Lung Cancers



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in the pipeline are not biomarker selected. Further research in ADC biomarkers will be crucial to maximize the potential of ADCs as a precision medicine by targeting patients most likely to benefit. Thoracic oncology clinicians will soon need to be familiar with the use of ADCs, including management of their toxicities, as part of an expanded treatment armamentarium that offers new hope to patients with lung cancers.

Bob T. Li, MD, PhD, MPH

Dr. Li is a medical oncologist and Chief Scientific Officer of MSK Direct at Memorial Sloan Kettering Cancer Center, New York.

Mélissa Prat, PhD

Dr. Prat is Oncology Translational Research Project Manager at Toulouse University Hospital, Toulouse, France.

Julien Mazières, MD, PhD

Dr. Mazières is Head of the Pulmonary Disease Department at Toulouse University Hospital and Program Leader of Thoracic Oncology at Toulouse University Institute of Cancer, Toulouse, France.

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Topic Update

Disparities in Lung Cancer Care and Outcomes

Kenneth L. Kehl, MD, MPH

Lung cancer is the leading cause of cancer death in the United States, but its burden is not distributed equally. Longstanding disparities exist across the continuum of care for patients with lung cancer, ranging from prevention to treatment for advanced disease. Better understanding of these patterns may inform interventions to improve population-level lung cancer outcomes.

Incidence and Prevention

Several populations suffer from a disproportionate incidence of lung cancer. Overall, lung cancer incidence is dropping as smoking rates decrease, but it is dropping faster for men than women, as men historically experienced a higher burden of lung cancer due to higher smoking rates. The incidence of lung cancer from 2014 to 2018 was higher in Black men than in White men, but the incidence was lower in Black women than in White women (*CA Cancer J Clin* 2022; 72:202). Notably, smoking prevalence and lung cancer incidence are both lower in Hispanic populations than in non-Hispanic Black or White populations (*Ann Am Thorac Soc* 2020; 17:399). Targeted smoking-cessation efforts could ameliorate disparities in lung cancer incidence; Black and Hispanic smokers have historically been less likely to receive smoking-cessation interventions (*Am J Prev Med* 2008; 34:404).

Diagnosis and Screening

Lung cancer screening with low-dose computed tomography decreases lung cancer–specific mortality but is underutilized. Efforts to optimize screening could ameliorate lung cancer outcome disparities. In the National Lung Screening Trial, a numerically greater mortality reduction was demonstrated in Black patients than in White patients (*Am J Respir Crit Care Med* 2015; 192:200). Focused screening efforts within Black populations therefore carry potential for mortality reduction.

Local Therapy

Early-stage non–small-cell lung cancer (NSCLC) is curable with high-quality local treatment including surgery or radiation therapy. However, the quality of therapy delivered for NSCLC varies by race. In a National Cancer Database (NCDB) study of patients with stage I NSCLC treated from 2004 to 2013, only 23% of patients received care that met at least one quality measure (anatomic resection within 8 weeks of diagnosis, negative surgical margins, and sampling of at least 10 lymph nodes); non-White patients were less likely to meet these metrics (*Ann Thorac Surg* 2017; 103:303). In addressing such racial disparities in local therapy, one system-based intervention in five cancer centers showed a reduced disparity between Black and White patients in receipt of curative treatment for early-stage NSCLC and improved care among all patients (*Cancer Med* 2019; 8:1095). In a Surveillance, Epidemiology, and End Results (SEER)–Medicare analysis of patients with stage I NSCLC, Black patients were less likely to receive any treatment, but after accounting for type of treatment, survival was similar to that observed in White patients (*J Thorac Cardiovasc Surg* 2019; 157:1670).

Adjuvant Therapy

Many patients with resected NSCLC who meet criteria for adjuvant chemotherapy do not receive it. In a recent NCDB study, patients with resected node-positive NSCLC were less likely to receive guideline-concordant multiagent adjuvant chemotherapy if they resided in rural areas, were uninsured, or had Medicaid coverage. Race/ethnicity was not a significant predictor of adjuvant chemotherapy in this cohort (*Ann Thorac Surg* 2020; 109:1512). Given the growing role of targeted therapy and immunotherapy in the adjuvant treatment of patients with NSCLC, it will be increasingly critical to understand hurdles to implementation of both

traditional adjuvant chemotherapy and diffusion of novel therapies across populations.

Workup and Treatment for Advanced Disease

Biomarker-directed targeted therapy and immunotherapy have transformed the treatment of advanced lung cancer over the last decade. However, many patients with advanced disease still do not receive any treatment, and for patients aged >65 years with stage IV NSCLC, increasing age, Black race, Medicaid eligibility, and residence in a high-poverty area are associated with decreased utilization of any systemic therapy (*Cancer Med* 2020; 9:2019c). Furthermore, disparities along multiple dimensions may impact dissemination of novel therapeutic strategies for lung cancer; for example, shortly after epidermal growth factor receptor biomarker testing became an important standard of care, rates of biomarker testing in the Medicare population were lower among Black patients and those with dual Medicaid coverage (*J Natl Cancer Inst* 2019; 111:431). Innovative health system interventions to lower structural barriers to advanced biomarker testing, such as facilitating biomarker testing regardless of site of care, could enable precision treatment for all patients.

Furthermore, longstanding disparities in clinical trial participation must be addressed to promote equitable lung cancer care. Efforts to design pipelines that facilitate clinical trial enrollment for underrepresented populations are needed to evaluate the benefits and risks of novel interventions across the diverse population of lung cancer patients.

Conclusion

Disparities in lung cancer care and outcomes have been widely characterized. To reduce the burden of lung cancer for all patients, it is now increasingly critical to design and evaluate health system interventions to ameliorate inequities in care.

Kenneth L. Kehl, MD, MPH

Dr. Kehl is a physician in the Thoracic Oncology Program at Dana-Farber Cancer Institute and Assistant Professor of Medicine at Harvard Medical School, Boston.

DISCLOSURES

Kenneth L. Kehl, MD, MPH, reports no disclosures.

Two Views

Two Approaches to Treating Resectable Non–Small-Cell Lung Cancer

Over the past 2 years, numerous exciting advances have been made in the care of patients with resectable non–small-cell lung cancer (NSCLC). We have become somewhat accustomed to the rapid integration of novel therapies in stage IV NSCLC over the past 7 years, but the same is not true for resectable disease, where the last "big thing" was the addition of platinum-based adjuvant therapy in 2005. In 2020, we saw the introduction of adjuvant osimertinib for completely resected stage II and IIIA *EGFR*-mutated NSCLC, and in 2021 and 2022, we have the exciting addition of immunotherapy to chemotherapy in both the adjuvant and neoadjuvant settings. Here, two prominent thoracic surgeons review the recent evidence for each approach in resectable NSCLC patients. This is not a pro–con debate and should not be such at any local tumor board; rather, these are two exciting new treatment options, and decisions on which approach to take should be personalized to each patient and treatment setting.

– Jessica Donington, MD, Editor

Adjuvant Immunotherapy for Resectable Non–Small-Cell Lung Cancer

Nasser Altorki, MD

In a cosmic nanosecond, or just 22 months in earthlings' time, adjuvant therapy for resected non–small-cell lung cancer (NSCLC) underwent a remarkable transformation. First came the much-anticipated results of the ADAURA trial that led to FDA approval of adjuvant osimertinib for patients with completely resected, stage IB–IIIA NSCLC with *EGFR* exon 19 deletions or exon 21 L858R mutations (*N Engl J Med* 2020; 383:1711). Exactly 1 year later, IMpower010 stepped up to the plate and hit a home run with adjuvant atezolizumab (*Lancet* 2021; 398:1344). Finally, in March 2022, investigators of KEYNOTE-091 reported significantly longer disease-free survival after adjuvant pembrolizumab (*Ann Oncol* 2022; 33:451). Key details and findings of IMpower010 and KEYNOTE-091 are summarized here.

IMPOWER010

The trial, for which I played an investigator role, randomized 1005 patients who had complete resection of stages IB–IIIA NSCLC followed by up to four cycles of cisplatin-based adjuvant chemotherapy to receive either adjuvant atezolizumab or best supportive care (*Lancet* 2021; 398:1344). The primary endpoint was disease-free survival (DFS), which was tested in the target population of patients with stages II–IIIA whose tumors expressed programmed death ligand 1 (PD-L1) on 1% or more of tumor cells (n=476), then in all patients in the stage II–IIIA population (n=882), and finally in the intention-to-treat (ITT) population (stages IB–IIIA; n=1005).

At the only planned interim analysis, DFS in the target population was significantly longer in patients treated with adjuvant atezolizumab, corresponding to a 34% reduction in the risk of recurrence, new primary NSCLC, or death compared with those receiving best supportive care. In all patients with stage II–IIIA regardless of PD-L1 expression, adjuvant atezolizumab conferred a significant 21% reduction in the risk of NSCLC recurrence or death compared with best supportive care. In the ITT population, DFS was numerically but not statistically significantly improved with atezolizumab. In patients with PD-L1–expressing, stage II–IIIA tumors, the 3-year DFS was 60% in the atezolizumab arm and 48% after best supportive care. For the key secondary endpoint of DFS in patients with stages II–IIIA whose tumors expressed PD-L1 in

at least 50% of tumor cells, the hazard ratio was an astonishing 0.43 (95% confidence interval, 0.27–0.68).

The trial results led to FDA approval of adjuvant atezolizumab following complete resection and platinum-based chemotherapy in patients with stage II–IIIA NSCLC whose tumors express PD-L1 in ≥1% of tumor cells as determined by Ventana's PD-L1 SP263 assay.

KEYNOTE-091

The next adjuvant immunotherapy trial to publish its findings was KEYNOTE-091 (PEARLS; NCT02504372), a global phase 3 trial that randomly allocated 1177 patients with completely resected, stage IB–IIIA NSCLC to either adjuvant pembrolizumab or placebo (*Ann Oncol* 2022; 33:451). Unlike IMpower010, the use of adjuvant chemotherapy was strongly encouraged but not mandated prior to randomization. The trial's dual primary endpoints were DFS in the overall patient population irrespective of PD-L1 expression and in patients with tumors expressing PD-L1 in at least 50% of tumor cells.

In comparison with patients in the placebo arm, patients in the adjuvant pembrolizumab arm had a statistically significant and clinically meaningful 24% reduction in the risk of disease recurrence or death, meeting one of the trial's coprimary endpoints. DFS at 18 months was also significantly longer after adjuvant pembrolizumab compared with after placebo (73.4% vs 63.4%). Paradoxically, DFS in patients whose tumors expressed PD-L1 in at least 50% of tumor cells was comparable in the pembrolizumab and placebo arms. The 18-month DFS was 71.7% after adjuvant pembrolizumab and 70.2% in the placebo group.

The impressive results of IMpower010 and KEYNOTE-091 inevitably raise several important questions: What is the optimal regimen for patients with tumors that do not express PD-L1? Are there biomarkers allowing us to more accurately select those patients most likely to benefit from treatment? Although more work remains to be done to answer these questions, it is now evident that molecular testing for patients with early-stage NSCLC is no longer optional but necessary and should be a marker of best practice if not an outright standard of care.

Neoadjuvant Chemotherapy and Immunotherapy for Resectable Non–Small-Cell Lung Cancer

Jonathan D. Spicer, MD, PhD

Surgery is the backbone of curative treatment for patients with resectable non–small-cell lung cancer (NSCLC), though we recognize the common systemic nature of this disease and the vital importance of perioperative systemic therapy (*N Engl J Med* 1994; 330:153 and *J Natl Cancer Inst* 1994; 86:673). Numerous studies have established the survival benefit of systemic treatments whether administered before or after resection in patients with resectable stage II or III NSCLC (*J Clin Oncol* 2008; 26:3552 and *Lancet* 2014; 383:1561). During the 30 years since the concept of multimodality therapy was introduced into NSCLC care, two recurring themes have emerged: (1) upfront surgery is the dominant approach and (2) patients with stage-eligible disease who undergo upfront surgery frequently do not go on to receive indicated adjuvant therapy (*JAMA Oncol* 2022 Mar 17; [e-pub]). Now, for the first time in over 20 years, we have strongly positive phase 3 data for patients with resectable NSCLC utilizing a neoadjuvant strategy (*Lancet Oncol* 2021; 22:e501).

Earlier this year, the CheckMate 816 team, of which I am a surgical representative, presented the results of this study comparing neoadjuvant chemotherapy and nivolumab with chemotherapy alone followed by surgery in patients with stage IB–IIIA NSCLC without known sensitizing *EGFR* mutations or *ALK* alterations (*N Engl J Med* 2022; 386:1973. See the NEJM Research Summary on page 13). The trial was powered for overall survival to be tested hierarchically if its two primary endpoints, the rate of pathological complete response (PCR) and event-free survival (EFS), were both found to be positive. Both

primary endpoints were strongly positive in favor of chemotherapy and nivolumab, with a 14-fold increased likelihood of PCR and an 11-month greater EFS compared with chemotherapy alone (hazard ratio for canceled surgery, recurrence, or death, 0.63; 97.38% confidence interval, 0.43–0.91).

In terms of overall survival, there was a numerical improvement of 12 percentage points at the 24-month interim analysis for the group receiving chemotherapy and nivolumab, with a hazard ratio of 0.57 (99.67% CI, 0.30–1.07). Together, the survival outcomes are extremely promising, and the surrogate value of PCR seems to be supported, as patients in both arms who developed a PCR demonstrated vastly superior EFS compared with patients without PCR. Although the study stratified enrollment of patients by stage, programmed death ligand 1 (PD-L1) expression, and sex, it was not powered to detect significant differences in efficacy across these strata. Hence, the subgroup analyses, though interesting for signal finding, are not definitive in terms of deciding if chemotherapy and nivolumab should only be used within specific subgroups.

Attrition to surgery is front of mind for both surgeons and patients alike. Patients who received chemotherapy and nivolumab were more likely to proceed to surgery than those who received chemotherapy alone. Furthermore, those patients who cannot proceed to surgery have excellent local control options via radiation therapy, and for those rare patients who develop metastasis during neoadjuvant chemoimmunotherapy, surgery would likely not have been a valuable therapeutic intervention. Importantly, 94% of patients treated with neoadjuvant chemotherapy and nivolumab completed all prescribed cycles of treatment and did not have an increased rate of adverse events as compared with patients undergoing chemotherapy alone. Finally, the administration of chemotherapy and nivolumab prior to surgery resulted in less extensive and less invasive surgery, with a higher rate of complete resection as compared with chemotherapy alone. No preoperative therapy or intraoperative technology has been shown to enable such important effects on the conduct of surgery for patients with resectable NSCLC.

If we are to cure more patients with resectable, locally advanced NSCLC, optimizing administration of systemic therapy and improving the quality of the patient's surgical experience will be paramount to success. CheckMate 816 paves the way for these goals to be achieved, but it will require thoracic oncology teams to reform their approach to managing resectable patients. Specifically, at a minimum, these teams will require information on complete staging, tissue diagnosis, PD-L1 testing, and molecular profiling to select the optimal therapeutic strategy to achieve the desired goal of cure.

Nasser Altorki, MD

Dr. Altorki is Vice Chairman of the Department of Cardiothoracic Surgery, Chief of the Division of Thoracic Surgery, the David B. Skinner Professor in Thoracic Surgery, and Program Leader of the Experimental Therapeutics Program at Meyer Cancer Center of Weill Cornell Medicine, New York.

Jonathan D. Spicer, MD, PhD

Dr. Spicer is Medical Director of the McGill Thoracic Oncology Network and a thoracic surgeon at McGill University Health Center, Montreal, Canada.

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NEJM Research Summary

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

Forde PM et al. DOI: 10.1056/NEJMoa2202170

CLINICAL PROBLEM

In phase 2 studies involving patients with resectable non–small-cell lung cancer (NSCLC), nivolumab-based neoadjuvant regimens showed promising clinical activity with respect to pathological complete response, survival, and safety. Additional data confirming those results are needed.

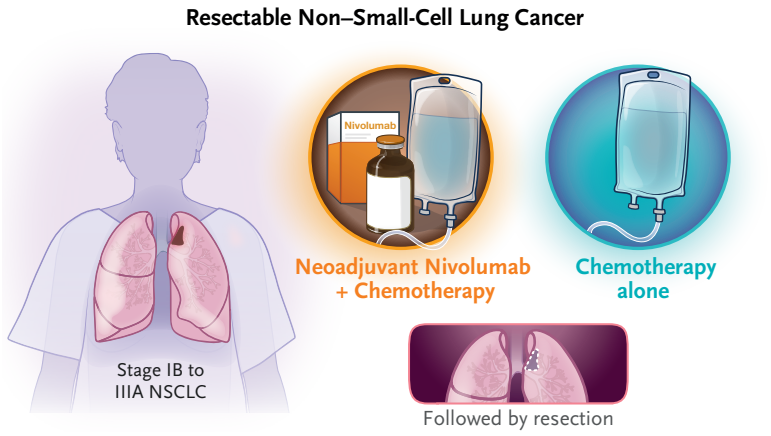
CLINICAL TRIAL

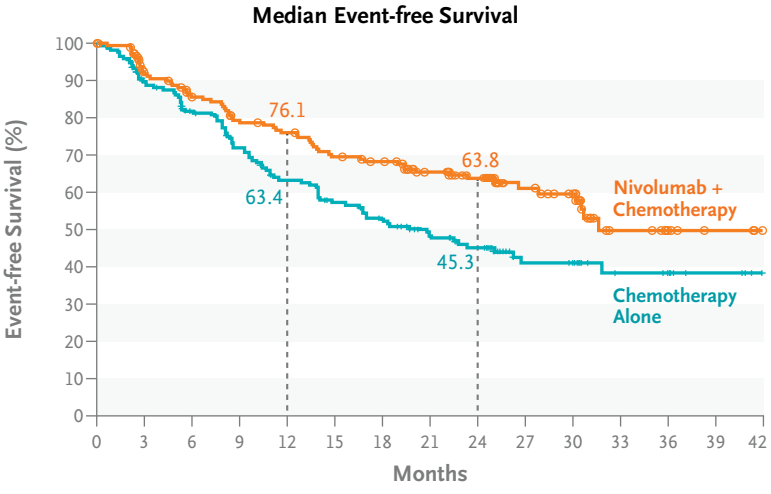
Design: An international, phase 3, randomized, open-label trial examined the efficacy and safety of neoadjuvant nivolumab plus chemotherapy, as compared with chemotherapy alone, in adult patients with stage IB to IIIA NSCLC.

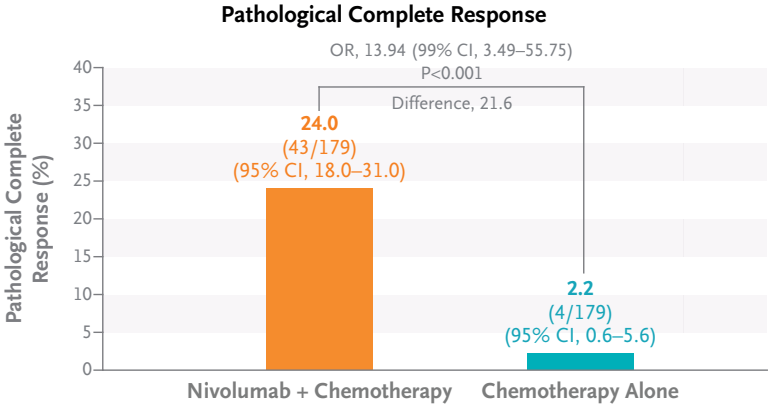
Intervention: 358 patients were randomly assigned to receive either neoadjuvant nivolumab (360 mg) plus platinum-doublet chemotherapy (every 3 weeks for three cycles) or platinum-doublet chemotherapy alone, followed by resection. The two primary end points were event-free survival and pathological complete response.

RESULTS

Efficacy: During a minimum follow-up of 21 months, median event-free survival was significantly longer with nivolumab plus chemotherapy than with chemotherapy alone. The percentage of patients with a pathological complete response also favored nivolumab plus chemotherapy.







Safety: The incidence of grade 3 or 4 treatment-related adverse events was similar in the two groups; neutropenia and decreased neutrophil count were the most common events.

LIMITATIONS AND REMAINING QUESTIONS

- More than 60% of the patients had stage IIIA disease; longer follow-up may be warranted to assess the benefits of neoadjuvant nivolumab in patients with NSCLC with a better prognosis.
- Continued follow-up is needed to evaluate the benefits with respect to overall survival, a key secondary end point.

CONCLUSIONS

Among patients with resectable NSCLC, neoadjuvant nivolumab plus chemotherapy was superior to chemotherapy alone with respect to event-free survival and pathological complete response, with no increase in adverse events.

NEJM Journal Watch Summary

Benefits of Including More Black Individuals in Lung Cancer Screening

In a statistical modeling study, increasing the proportion of Black individuals in the National Lung Screening Trial population increased the relative mortality benefit of low-dose CT screening.

In the randomized National Lung Screening Trial (NLST), screening by low-dose computed tomography (LDCT) was associated with a 20% relative reduction in lung cancer death compared with screening by chest radiography (*N Engl J Med* 2011; 365:395). Only 4.4% of the NLST study population was Black. Given that Black individuals have the highest rates of lung cancer death, understanding whether findings would differ if the proportion of Black individuals in the screening population was higher is of interest. In this secondary analysis of NLST data, researchers used statistical modeling to estimate screening outcomes in hypothetical populations with varying distributions of Black individuals, women, and current smokers.

Increasing the percentage of Black participants in the hypothetical screening population from 4.4% to 13.4%, a number reflective of U.S. census data, resulted in a greater relative reduction of lung cancer mortality with LDCT screening; the hazard ratio improved from 0.84 to 0.82. Further relative reductions in lung cancer mortality with LDCT screening were found when the proportion of men or current smokers was increased simultaneously with the proportion of Black individuals.

Comment

This study suggests the mortality benefit of LDCT lung cancer screening programs could be further heightened if more Black people who were eligible could undergo screening. This finding underscores the urgency for taking action to eliminate barriers and improve access to potentially lifesaving CT screening for Black smokers.

Jyoti D. Patel, MD, FASCO

Dr. Patel is Professor of Medicine at Northwestern University, where she is Medical Director of Thoracic Oncology and Assistant Director for Clinical Research at the Robert H. Lurie Comprehensive Cancer Center, and is Associate Vice-Chair of Clinical Research in the Department of Medicine. She reports consultant roles with AbbVie, Bristol Myers Squibb, and AstraZeneca.

Prosper AE et al. Association of inclusion of more Black individuals in lung cancer screening with reduced mortality. **JAMA Netw Open** 2021 Aug 24; 4:e2119629. (https://doi.org/10.1001/jamanetworkopen.2021.19629)

NEJM Journal Watch Summary

Trends in Lung Cancer Presentation and Survival in the Era of Screening

Early-stage diagnoses and all-cause survival accelerated in 2014, after CT screening was recommended for high-risk patients.

In December 2013, the U.S. Preventive Services Task Force recommended low-dose computed tomography (CT) screening for lung cancer in high-risk individuals (*Ann Intern Med* 2014; 160:330). Randomized trials demonstrated that malignancies were diagnosed at earlier stages and survival improved in screened groups, but these effects have not been demonstrated in real-world populations.

Using U.S. national oncology databases, investigators identified >750,000 patients who received diagnoses of non–small-cell lung cancer (NSCLC) between 2010 and 2018. Among these patients, the percentage who received diagnoses of stage I NSCLC and median all-cause survival increased significantly more rapidly from 2014 to 2018 than from 2010 to 2013; in other words, rates of change in early diagnosis and survival increased starting around 2014. By 2018, the proportion of cases diagnosed at stage I had increased to 36%, and median all-cause survival had increased to 28 months. In 2018, for the first time, white patients more often received diagnoses of stage I than of stage IV NSCLC; however, stage IV cases continued to exceed stage I cases in other ethnic groups.

Comment

In this study, the observed accelerated rate of early-stage diagnosis likely is attributable to screening. Screening also might have contributed to longer survival, but advances in treatment also might be a factor, and lead-time bias from screening could inflate survival data artificially. The disturbing persistence of racial and economic disparities in rates of early diagnosis likely is related to unequal access. With studies suggesting that only around 5% of eligible patients were screened in 2015, substantial opportunities undoubtedly remain to limit lung cancer mortality and reduce disparities through more accessible screening.

Bruce Soloway, MD

Dr. Soloway is Associate Professor of Family Medicine and Attending Family Physician at Montefiore Medical Center, Albert Einstein College of Medicine, New York. He reports no disclosures.

Potter AL et al. Association of computed tomography screening with lung cancer stage shift and survival in the United States: Quasi-experimental study. **BMJ** 2022 Mar 30; 376:e069008. (https://doi.org/10.1136/bmj-2021-069008)

Melzer AC and Triplette M. Screening high risk populations for lung cancer: Early evidence of a stage shift suggests real world benefits. **BMJ** 2022 Mar 30; 376:o666. (https://doi.org/10.1136/bmj.o666)

NEJM Journal Watch Summary

What Is the Role of Radiotherapy in Early-Stage Lung Cancer?

The use of radiotherapy as a treatment option is increasing, underscoring the need for radiation oncologists to be involved in the multidisciplinary management of patients with pulmonary nodules.

The number of individuals eligible for lung cancer screening has nearly doubled since the U.S. Preventive Services Task Force recently expanded guidelines to include individuals 50 to 80 years of age who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. Moreover, the number of pulmonary nodules discovered incidentally on computed tomography during screening has also markedly increased.

For patients with pulmonary nodules requiring treatment, the role of thoracic surgery is well established, but the role of radiotherapy is unclear. To address this issue, investigators conducted a prospective cohort study of 1150 patients who presented with pulmonary nodules at a lung cancer screening clinic during a 7-year period (2012–2019).

Among 196 patients with incidental nodules requiring treatment, 136 (69%) underwent surgery and 60 (31%) underwent stereotactic body radiotherapy (SBRT). Among 41 patients with screen-detected nodules requiring treatment, 31 (76%) underwent surgery and 10 (24%) underwent SBRT. Among patients who underwent SBRT, 2-year overall survival was 87% and 2-year metastasis-free survival was 94%.

Comment

As the number of patients with screen-detected or incidental pulmonary nodules has increased, multidisciplinary evaluation has become a widely recommended measure to ensure their effective care. Yet, although multidisciplinary teams have traditionally included thoracic radiologists, pulmonologists, and thoracic surgeons in this setting, they have not tended to include radiation oncologists. Because SBRT is a valuable treatment option for a growing number of patients with screen-detected or incidental nodules, the expertise that radiation oncologists can provide should be included in their multidisciplinary management.

Jyoti D. Patel, MD, FASCO

Dr. Patel is Professor of Medicine at Northwestern University, where she is Medical Director of Thoracic Oncology and Assistant Director for Clinical Research at the Robert H. Lurie Comprehensive Cancer Center, and is Associate Vice-Chair of Clinical Research in the Department of Medicine. She reports consultant roles with AbbVie, Bristol Myers Squibb, and AstraZeneca.

Milligan MG et al. Incidence of radiation therapy among patients enrolled in a multidisciplinary pulmonary nodule and lung cancer screening clinic. **JAMA Netw Open** 2022 Mar 31; 5:e224840. (https://doi.org/10.1001/jamanetworkopen.2022.4840)

NEJM Journal Watch Summary

Segmentectomy Is Supported as Standard of Care for Small, Peripheral Non–Small-Cell Lung Cancer

In a randomized trial, segmentectomy was noninferior to lobectomy in terms of overall survival.

Surgical resection via lobectomy is the standard treatment for patients with early-stage lung cancer. However, indications for sublobar resection of early-stage lung cancer have recently expanded to include small-sized, peripheral tumors with no lymph node involvement. Now, Japanese oncology groups have assessed whether segmentectomy is noninferior to lobectomy in treatment of clinical stage IA, small-sized, peripheral non–small-cell lung cancer (NSCLC).

This phase 3, randomized, controlled trial included 1106 patients with the following findings on contrast-enhanced computed tomography: a single tumor not located in the middle lobe, the center of which was in the outer third of the lung field; tumor diameter ≤2 cm; and no evidence of lymph node metastasis. The primary endpoint was overall survival.

Patients who underwent segmentectomy had a significantly higher 5-year overall survival (94.3% vs. 91.1%). The secondary endpoint of 5-year, relapse-free survival was nearly identical between the two groups (88.0% in segmentectomy vs. 87.9% for lobectomy). The probability of local recurrence in the segmentectomy group was approximately doubled compared with the lobectomy group (11% vs. 5%). At a median follow-up of 7.3 years, the greater number of deaths in the lobectomy group (83 vs. 58) was not the result of the primary NSCLC, but rather other cancers (including second primary lung cancer) and non–lung-cancer causes, including respiratory and cerebrovascular diseases.

Comment

These findings demonstrate 5-year overall survival of greater than 90% in patients with clinical stage IA, small-sized, peripheral NSCLC who receive curative-intent surgery. In addition, this study indicates that segmentectomy should be the standard surgical procedure performed, instead of lobectomy, in these patients.

Jyoti D. Patel, MD, FASCO

Dr. Patel is Professor of Medicine at Northwestern University, where she is Medical Director of Thoracic Oncology and Assistant Director for Clinical Research at the Robert H. Lurie Comprehensive Cancer Center, and is Associate Vice-Chair of Clinical Research in the Department of Medicine. She reports consultant roles with AbbVie, Bristol Myers Squibb, and AstraZeneca.

Saji H et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): A multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. **Lancet** 2022 Apr 23; 399:1607. (https://doi.org/10.1016/S0140-6736(21)02333-3)

NEJM Journal Watch Summary

Oral Tyrosine Kinase Inhibitor for *EGFR* Exon 20-Insertion-Positive NSCLC

In a phase 1/2 trial, mobocertinib produced clinically meaningful and durable responses in patients with* EGFR*ex20ins-positive metastatic NSCLC.

Mobocertinib is a first-in-class irreversible tyrosine kinase inhibitor that was designed to selectively target in-frame *EGFR* exon 20 insertion (*EGFR*ex20ins) mutations in non–small-cell lung cancer (NSCLC). In a multicenter phase 1/2 nonrandomized study, 114 patients with *EGFR*ex20ins-positive NSCLC previously treated with platinum-based chemotherapy received mobocertinib (160 mg once daily) until disease progression or unacceptable toxicity.

At a median 14.2 months' follow up, the objective response rate by independent review — the primary endpoint — was 28% (95% confidence interval, 20%–37%). An additional 50% of patients had stable disease, for a disease control rate of 78%. The median duration of response was 17.5 months (95% CI, 7.4–20.3 months), median progression-free survival was 7.3 months (95% CI, 5.5–9.2 months), and median overall survival was 24.0 months (95% CI, 14.6–28.8 months). The most common treatment-related adverse events of any grade were diarrhea (91%), rash (45%), and paronychia (38%). Grade >3 adverse events occurred in 69% of patients and were considered treatment-related in 47%.

Adverse events led to dose reduction in 25% of patients and to treatment discontinuation in 17%, most commonly owing to diarrhea (4%), nausea (4%), vomiting (2%), decreased appetite (2%), and stomatitis (2%).

Comment

This study was the basis for the recent FDA approval of mobocertinib for the treatment of adult patients with locally advanced or metastatic *EGFR* exon 20 insertion–mutant metastatic NSCLC who have received prior platinum-based chemotherapy. Mobocertinib joins amivantamab, an EGFR-MET-bispecific antibody, as a treatment option in this subset of patients. Patients with *EGFR*ex20 insertion–positive NSCLC make up approximately 1% to 2% of the over 1.5 million patients worldwide with NSCLC. Mobocertinib represents an important treatment option for this group, but attention to toxicity will be crucial.

Jyoti D. Patel, MD, FASCO

Dr. Patel is Professor of Medicine at Northwestern University, where she is Medical Director of Thoracic Oncology and Assistant Director for Clinical Research at the Robert H. Lurie Comprehensive Cancer Center, and is Associate Vice-Chair of Clinical Research in the Department of Medicine. She reports consultant roles with AbbVie, Bristol Myers Squibb, and AstraZeneca.

Zhou C et al. Treatment outcomes and safety of mobocertinib in platinum-pretreated patients with EGFR exon 20 insertion–positive metastatic non–small cell lung cancer: A phase 1/2 open-label nonrandomized clinical trial. **JAMA Oncol** 2021 Dec 1; 7:e214761. (https://doi.org/10.1001/jamaoncol.2021.4761)

NEJM Journal Watch Summary

Mechanisms of Resistance to KRAS Inhibitors

A heterogeneous pattern of resistance was observed in both patient specimens and xenograft models.

The approval of sotorasib in 2021 was felt to be a watershed moment in cancer therapeutics, primarily because KRAS was considered an "undruggable" target for many years. RAS proteins are a family of prototypical oncogenes that are mutated in many human cancers. *KRAS* is the most frequently mutated isoform of *RAS* mutations (86%), and is mutated in 90% of pancreatic, 40% of colorectal, and 30% of lung cancers. Mutant KRAS has long been referred to as an undruggable target because of its unusual shape. Compared with other proteins, its relatively smooth protein structure meant that designing inhibitors to bind to surface grooves was difficult, stalling progress in drug development for many years. The FDA's accelerated approval of the KRAS inhibitor sotorasib was based on a phase 2 trial of 124 previously treated patients with KRAS G12C-mutated non–small cell lung cancer that demonstrated a response rate of 37%, median duration of response of 11 months, and progression-free survival of 6.8 months (*N Engl J Med* 2021; 384:2371).

Because resistance to targeted therapies inevitably develops, researchers sought to further understand mechanisms of resistance to KRAS GTPase inhibitors. They evaluated matched pre- and posttreatment specimens from 43 patients treated with sotorasib. In 27 of the 43 patients who developed resistance, multiple treatment-emergent alterations occurred in both *KRAS* and other genes, including *NRAS*, *BRAF*, *EGFR*, and *MYC*. The researchers found similar treatment-emergent mutations in xenograft models.

Comment

These data suggest a heterogenous pattern of alterations associated with resistance to KRAS G12C inhibition in both clinical and preclinical settings. The lack of a dominant resistance alteration makes finding a single second treatment strategy challenging, but it may be that these treatment-emergent mutations could inform investigation of next therapies. Patients who have new mutations in *KRAS*, *NRAS*, or *BRAF* may benefit from co-targeting *ERK* signaling. We will likely see biomarker-driven prospective trials to determine best treatments for patients with progression on KRAS G12C inhibitor monotherapy.

Jyoti D. Patel, MD, FASCO

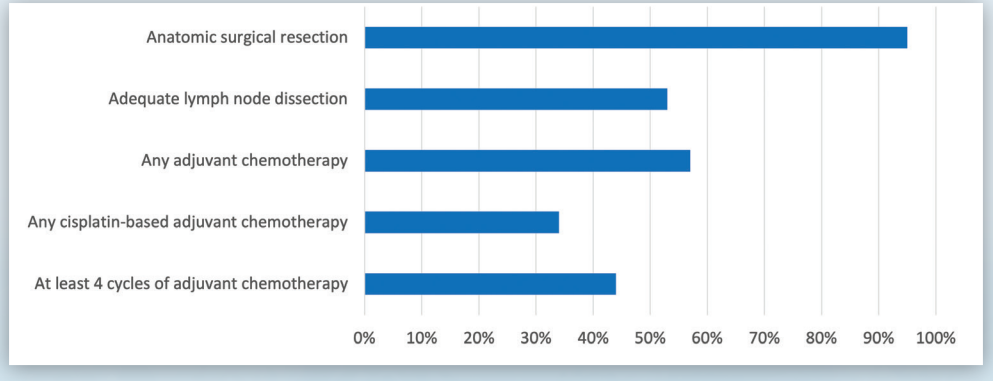
Dr. Patel is Professor of Medicine at Northwestern University, where she is Medical Director of Thoracic Oncology and Assistant Director for Clinical Research at the Robert H. Lurie Comprehensive Cancer Center, and is Associate Vice-Chair of Clinical Research in the Department of Medicine. She reports consultant roles with AbbVie, Bristol Myers Squibb, and AstraZeneca.

Zhao Y et al. Diverse alterations associated with resistance to KRAS(G12C) inhibition. **Nature** 2021; 599:679. (https://doi.org/10.1038/s41586-021-04065-2)

Visual Summary

Are Patients Receiving Guideline-Concordant Treatment for Lung Cancer?

Percentage of 2833 U.S. patients with stage IB–IIIA non–small-cell lung cancer (tumors ≥4 cm and/or positive lymph nodes) enrolled in the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) screening study who received guideline-recommended treatments



Comment

This study reveals a low rate of guideline-concordant lung cancer care at centers across the United States. These patients were being considered for clinical trial participation, and clinical trial participants are typically younger and have better performance status and fewer comorbid conditions than patients in routine care; hence, they are more likely to receive guideline-recommended therapies. It is surprising that rates of guideline-recommended therapy for patients recruited to ALCHEMIST were not substantially higher than those reported in broader population-based cohorts.

This study also highlights the difficulties of extrapolating clinical trial findings to broader patient populations. For example, the EGFR tyrosine kinase inhibitor osimertinib and the PD-L1 inhibitor atezolizumab have been integrated into routine adjuvant therapy based on trials in which the primary endpoint was disease-free survival rather than overall survival. If nodal dissection were inadequate in those trials, that could mean that micrometastatic disease was being controlled during adjuvant therapy.

Lastly, it is important to identify barriers to guideline-concordant care and implement strategies to address inadequate treatment.

Jyoti D. Patel, MD, FASCO, reviewing Kehl KL et al. *JAMA Oncol* 2022; 8:717

Dr. Patel reports consultant/advisory board roles with AbbVie, Bristol Myers Squibb, and AstraZeneca.