Early-Stage Lung Cancer Findings
End a Debate, Put Focus on Next Steps

New data have resolved one of oncology’s long-standing debates: Adjuvant therapy in early-stage, non–small-cell lung cancer (NSCLC) does improve survival significantly and probably should become the standard of care, according to the findings of two major trials.

In one of the trials, led by the National Cancer Institute of Canada (NCIC), there was an absolute survival benefit of 15% after 5 years for patients receiving chemotherapy. In the other, led by the Cancer and Leukemia Group B (CALGB), the absolute benefit was 12% after 4 years.

“Our belief is that the findings will lead to changes in therapy,” said Bruce Johnson, M.D., of Dana-Farber Cancer Institute, Boston, speaking at the June meeting of the American Society of Clinical Oncology (ASCO) in New Orleans, where the late-breaking abstracts were presented.

Katherine Pisters, M.D., of the University of Texas M. D. Anderson Cancer Center, Houston, agreed: “Adjuvant chemotherapy is indeed a new standard of care for early-stage non–small-cell lung cancer.”

The findings set the stage for a new set of questions, as experts considered why the results differed from those of earlier studies, their implications for practice, and next steps in clinical research.

Up to now, surgery alone has been the standard of care for patients with early-stage NSCLC. Over the past decade, several large multicenter trials have looked at adjuvant therapy, but their results have been negative or inconclusive or shown only a modest survival advantage. The result has been the long debate over whether there was enough evidence to justify the use of adjuvant therapy in early-stage NSCLC.

In contrast, the findings of the two newly reported trials were unambiguous. In the NCIC trial, patients with stage IB and II disease, whose tumors had been completely removed, were randomly assigned to receive either post-surgical therapy with cisplatin and vinorelbine or to observation. At 5 years, 69% of patients in the chemotherapy arm were alive compared with 54% in the control group.

The other trial (CALGB 9633) included only patients with stage IB disease, and they were randomly assigned to receive either carboplatin and paclitaxel or no chemotherapy. After 4 years, 71% of patients who had received chemotherapy were alive compared with 59% of those who had surgery alone.

**Why the Difference?**

Two other large adjuvant trials have been reported in just the past few years. The Adjuvant Lung Project of Italy (ALPI) showed no difference in survival between its chemotherapy and control arms. And the International Adjuvant Lung Cancer Trial (IALT), presented at the ASCO meeting in 2003, showed an absolute survival benefit of just 4.1% for those receiving adjuvant therapy.

Why the difference between these results and those of the new trials? According to some experts, the narrower subset of early-stage patients who took part in the new trials may be part of the reason. The patient population was “well staged, well defined, and much tighter” than in previous trials, said Timothy Winton, M.D., the NCIC principal investigator. Participants in the two new trials were limited to those who had completely resected disease, stages IB or IIA. In contrast, IALT and ALPI enrolled patients with stages I–IIIA.

For some, the tightly defined patient population raised the issue of how applicable the findings are to all early-stage patients. “CALGB and NCIC told us that in very selected groups of patients, adjuvant therapy works. This is different from saying adjuvant therapy is for everyone,” said Giorgio Scagliotti, M.D., of the University of Torino in Italy.

To help extend the NCIC and CALGB findings, Scagliotti recommended a new meta-analysis of all the platinum-based adjuvant trials in early-stage NSCLC.

The patient population was not the only difference among the trials, however. The NCIC’s Frances Shepherd, M.D., of Princess Margaret Hospital in Toronto, pointed out that both the NCIC and CALGB trials used a third-generation drug along with the platinum drugs and that toxicity was relatively low. “I think it was the drugs, mainly [that made the difference],” she said. Shepherd also pointed out that compliance with therapy in the NCIC and CALGB trials was relatively high and toxicity low compared with earlier trials.

**Next Steps**

While researchers may continue to analyze the differences between the trials, it seems clear that most clinicians will now be considering adjuvant therapy for most early-stage patients. However, deciding which patients are most likely to benefit is a question that is likely to get more attention. Pisters, who was appointed by ASCO to discuss the two new trials, said that future trials should focus on “better selection of patients through staging and biology.”
Another area of research likely to be affected by the new data is neoadjuvant therapy. Paul Bunn, M.D., of the University of Colorado Health Science Center in Denver, noted that the control arms of such trials are now in question. One Southwestern Oncology Group trial that was comparing neoadjuvant chemotherapy to surgery alone has closed because the surgery-alone arm can no longer be considered ethical, he said.

“I’d like to see a trial comparing neoadjuvant and adjuvant therapy,” Bunn said. “There’s reason to think that neoadjuvant may be better.”

In the meantime, attention is also turning to the next generation of adjuvant treatments. There will probably be a move toward combining platinum-based regimens with other newer agents, predicted Scott Saxman, M.D., of the National Cancer Institute’s Cancer Therapy Evaluation Program.

“I don’t think there will be a lot of interest in comparing the various platinum combinations or different administration schedules,” he said. “The next series of trials will probably involve platinum-based combinations plus a targeted agent.”

The Canadian cancer institute is already leading one such trial, comparing gefitinib (Iressa) to placebo after surgery in patients with early-stage disease, stages IB–III, who have had platinum-based chemotherapy or no chemotherapy. The NCIC’s Shepherd said that about 300 patients have been enrolled in this trial so far, a quarter of the 1,200 needed.

Gefitinib, which works by interfering with the signaling pathway of the epidermal growth factor receptor (EGFR), is similar in this respect to erlotinib (Tarceva), which improved survival in patients with advanced NSCLC in another major trial presented at the ASCO meeting. Erlotinib’s success could mean that it too is headed for the adjuvant setting. Dana-Farber’s Johnson, speaking at an ASCO media briefing, said that the findings are likely “to move erlotinib further up front [for use] earlier in treatment.”

On the other hand, erlotinib’s similarity to gefitinib may discourage such a trial. “In my opinion, there is currently not a reason to believe they are sufficiently different that we need to test both in the same clinical situation,” Saxman said.

Combining chemotherapy with a different kind of EGFR-targeted drug is another possible scenario, however. The antibody cetuximab (Erbitux), for example, works differently from gefitinib and erlotinib, blocking EGFR by binding to a portion of the receptor. It is currently being tested in NSCLC in several phase I and II trials.

A range of other targeted therapies have shown promise in lung cancer. Some, like farnesyl transferase inhibitors and an antisense compound called ISIS 3521, have had disappointing results. One agent still moving ahead, however, is bevacizumab (Avastin), now in a phase III trial for advanced NSCLC. This trial (ECOG 4598) completed accrual a few months ago, and results could be available next year. Depending on the outcome, bevacizumab may be a candidate for an adjuvant trial, said both Shepherd and Saxman.

The interest in targeted therapies is spurring related studies of markers to predict which subsets of patients will benefit from a particular therapy. In the gefitinib trial, for example, the researchers are collecting tissue from all patients and will test the samples for a newly identified EGFR mutation to see whether the mutation predicts for clinical benefit.

Many more efforts to link clinical outcomes to the biology of targeted therapies are likely to follow, in response to the need to know which patients have the target and whether variations in the target affect response. These efforts “will be a critical feature of future trials,” Saxman said.

—Caroline McNeil