Photo: Small cancerous tumor filling an alveolus of the human lung. Moredun Animal Health LTD/Photo Researchers, Inc.

COMMUNITY ONCOLOGY

PRESENTING CLINICAL TRIALS FOR PATIENT ENROLLMENT

A randomized phase III trial of BIBW 2992 versus chemotherapy as first-line treatment for stage IIIB/IV adenocarcinoma of the lung harboring an epidermal growth factor receptor-activating mutation

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LUX-Lung 3, an ongoing randomized, multicenter, open-label phase III trial, compares single-agent BIBW 2992 (afatinib) with standard pemetrexed/cisplatin chemotherapy as first-line treatment of stage IIIB/IV adenocarcinoma of the lung with epidermal growth factor receptor (EGFR)-activating mutations. BIBW 2992 is an investigational, orally administered irreversible EGFR-1 and human epidermal growth factor receptor-2 (HER2) tyrosine kinase inhibitor (TKI). The current trial (LUX-Lung 3) will randomize 330 patients in a 2:1 ratio to receive either BIBW 2992 or chemotherapy with pemetrexed/cisplatin. Patients will receive either BIBW 2992 at a starting dose of 40 mg once daily continuously or pemetrexed (500 mg/m^2 IV) and cisplatin (75 mg/m^2) on day 1 of 21-day cycles. Patients will receive 6 cycles of chemotherapy unless unacceptable toxicity occurs. BIBW 2992 will be given continuously until disease progression occurs. The primary endpoint is progression-free survival (PFS). Secondary endpoints include objective response, disease control assessed using Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and overall survival. Oncologists may obtain information on how to enroll patients from the National Institutes of Health's Web site (www.clinicaltrials.gov/ct2/show/NCT00949650).

Lung cancer is a leading cause of cancer-related deaths around the world. Unfortunately, most patients diagnosed with lung cancer already have advanced disease. Even among those initially found to have early-stage disease, the relapse rate is high following treatment with surgery.[1]

Treatment depends on the histology (small cell versus non-small cell) and the stage of the disease. The addition of adjuvant platinum-based

Acknowledgments: This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc (BIPI). BIPI reviewed the manuscript and provided scientific input throughout the development of the manuscript. The authors received no compensation related to the development of this manuscript. The authors wish to thank Brian Green, MSc, of Elsevier Oncology, for providing editorial support. Lecia V. Sequist, MD, MPH, provided manuscript drafts and gave final approval to publish the manuscript. Chih-Hsin James Yang, MD reviewed and provided comments and final approval to the manuscript.

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Commun Oncol 2010;7:1–4

Resources

Information on eligibility for this clinical trial and treatment

- National Institutes of Health: www.clinicaltrials.gov/ct2/show/NCT00949650

Patient resources

- CancerIndex: www.cancerindex.org
- Clinical Trials Search: www.clinicaltrialssearch.org
- National Cancer Institute: www.cancer.gov
- LUNGevity Foundation: e-mail to: info@lungevity.org

chemotherapy following resection of non small-cell lung cancers (NSCLCs) appears to prolong survival in patients with stage II or stage III disease.[2] Currently, the 5-year survival rate for patients with localized NSCLC is around 50%.[3]

Chemotherapy alone, or in combination with radiation therapy, is the standard treatment for unresectable and metastatic NSCLCs. Although platinum-based doublets are the foundation for treating NSCLC, there is no single standard regimen, and[4–6] the addition of bevacizumab (Avastin) may provide an additional survival benefit in patients with a nonsquamous histology.[7]

The role of targeted therapies

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase present in many normal cells and plays an important role in the regulation of cell growth, differentiation, migration, and apoptosis. EGFR is one of four members of the ErbB family of receptors, which also includes human epidermal growth factor receptor-2 (HER2)/C-*neu*, HER3, and HER4.[8,9]

Following binding to one of its ligands, EGFR undergoes dimerization and activation, which involves stimulation of the intrinsic protein tyrosine kinase activity of the receptor and autophosphorylation of several tyrosine residues; this process results in a series of changes in the cell that affect a number of metabolic processes, including cell proliferation, motility, and survival.[9] Homodimer and heterodimer formation occur within the ErbB family and are thought to contribute to additional regulation and specificity of cellular processes. Overexpression of EGFR and its ligands is a characteristic of several cancers (including lung cancer) and is associated with a poor prognosis.[9–12]

Targeted therapy refines the approach to cancer treatment by interfering with known vital pathways in oncogenesis and apoptosis. Given its central role in lung cancer biology, oral inhibitors of EGFR have been developed. First-generation EGFR tyrosine kinase inhibitors (TKIs) include gefitinib (Iressa) and erlotinib (Tarceva); in NSCLC; the response rate to first-generation EGFR TKIs is approximately 12%–20%.[13–15] However, mutations in the EGFR tyrosine kinase (TK) domain define a subpopulation of NSCLC tumors that are highly dependent on EGFR signaling for their continued survival.[12,16,17] Blocking EGFR via TKIs in cancers with an EGFR mutation has led to response rates of 55%–75% and improved clinical outcomes.[18–20] Three randomized controlled trials[21–23] have now demonstrated improved progression-free survival in patients with EGFR mutations treated with gefitinib compared with platinum and taxane-based chemotherapy. However, resistance to first-generation EGFR TKIs generally occurs after 6–9 months, primarily through the development of a secondary resistance mutation in EGFR called T790M.

Important questions remain regarding first-line use of EGFR TKIs in patients with EGFR mutations. 1) Can the results obtained in these studies (all of which were performed in Asia) be extrapolated to all patients? 2) Will similar results be obtained with other EGFR TKIs, including those that may have activity against the T790M resistance mutation? 3) How will EGFR TKIs compare with pemetrexed (Alimta)-based chemotherapy regimens, which may have superior activity in patients with adenocarcinoma?

What is BIBW 2992?

BIBW 2992 is an investigational, orally administered, dual receptor TKI of EGFR-1 and HER2. It binds irreversibly to EGFR, thereby inhibiting EGFR signaling for the life of the receptor. It is currently under study as a possible first-line treatment of NSCLC in patients with EGFR mutations.

Rationale for investigating BIBW 2992 in NSCLC

At the 2010 ASCO meeting, Yang et al[24] presented preliminary results from an open-label multicenter phase II study in Taiwan and the United States of 129 patients with known EGFR mutations who were TKI-naive and treated with BIBW 2992 at a starting dose of 40 or 50 mg once daily (LUX-Lung 2). Objective response rate and disease control rate was 62% and 94%, respectively, for del19; 52% and 85% for L858R; and 43% and 78% for other mutations based on investigator assessment. Median PFS was estimated to be 12 months (95% CI: 10-19.2) for the overall group, 12 months (95% CI: 10-19.2) in del19, 16.3 months (95% CI:10-Inf) in L858R, and 15.6 months (95% CI:10-19.2) when combined. Diarrhea and rash/acne were the most commonly observed adverse events (95% of patients each; 18% and 19% were Grade 3, respectively). Further investigation of BIBW 2992 in the LUX-Lung 3 trial is currently underway. The efficacy and safety of BIBW 2992 have not been established.

What is the LUX-Lung 3 trial?

The LUX-Lung 3 trial is a randomized, multicenter, open-label phase III trial designed to evaluate the efficacy of orally administered,

single-agent BIBW 2992 compared with pemetrexed/cisplatin standard chemotherapy as first-line treatment of patients with stage IIIB/IV adenocarcinoma of the lung with an EGFR-activating mutation. The trial is being performed by investigators who specialize in the treatment of lung cancer. Study selection and exclusion criteria are shown in Table 1. Written informed consent is being obtained prior to randomization. Approximately 2,200 patients are being screened for the trial to identify 330 eligible patients. All patients are required to provide a tumor biopsy for EGFR mutation testing.* Eligible patients will be randomized in a 2:1 ratio to receive either BIBW 2992 (arm A) or chemotherapy with pemetrexed/cisplatin (arm B). Patients will be assigned to receive either:

BIBW 2992 at a starting dose of 40 mg once daily, OR pemetrexed (500 mg/m^2 IV) and cisplatin (75 mg/m^2) on day 1 every 21 days (Figure 1).

Patients will receive 6 cycles of chemotherapy unless unacceptable toxicity occurs. After 1 cycle (3 weeks) of treatment, patients in the BIBW 2992 arm who have no or minimal drug-related adverse events will have their dose increased to 50 mg once daily; the drug will be given continuously until disease progression occurs. In the event of drug-related AEs, the dose will be reduced in increments of 10 mg, with the lowest dose being 20 mg. The primary endpoint is PFS. Secondary endpoints include objective response, disease control assessed using Response Evaluation Criteria In Solid Tumors (RECIST) criteria,[25] and overall survival. Assessments of response will be carried out at 6 weeks, 12 weeks, and every 6 weeks thereafter until disease progression or study withdrawal occurs. After 48 weeks, assessments of response will be carried out every 12 weeks until disease progression or study withdrawal

* This testing will be performed as part of the study.

TABLE 1

Study selection criteria for LUX-Lung 3 trial

Inclusion criteria

- Pathologically confirmed diagnosis of stage IIIB/IV adenocarcinoma of the lung. Patients with mixed histology are eligible if adenocarcinoma is predominant.
- EGFR mutation detected by central laboratory analysis of tumor biopsy material
- Measurable disease according to RECIST 1.1
- ECOG performance status of 0 or 1
- Age >18 years
- Life expectancy of at least 3 months
- Written informed consent that is consistent with ICH–GCP guidelines

Exclusion criteria

- Prior chemotherapy for relapsed and/or metastatic NSCLC. Neoadjuvant/adjuvant chemotherapy is permitted if at least 12 months has elapsed between the end of chemotherapy and randomization.
- Prior treatment with EGF- targeting small molecules or antibodies
- Radiotherapy or surgery (other than biopsy) within 4 weeks prior to randomization
- Active brain metastases (defined as stable for < 4 weeks and/or symptomatic and/or requiring treatment with anticonvulsants or steroids and/or leptomeningeal disease)
- Any other current malignancy or malignancy diagnosed within the past 5 years (other than nonmelanomatous skin cancer and in situ cervical cancer)
- Known preexisting interstitial lung disease
- Significant or recent acute gastrointestinal disorders with diarrhea as a major symptom (eg, Crohn's disease, malabsorption, or CTC grade > 2 diarrhea of any etiology)
- Significant cardiovascular diseases
- Any concomitant serious illness or organ dysfunction that could compromise patient safety
- Inadequate kidney or liver function tests
- Inadequate blood counts
- Active hepatitis B infection, active hepatitis C infection, or known HIV carrier
- Any contraindications for therapy with pemetrexed, cisplatin, or dexamethasone
- Known hypersensitivity to BIBW 2992 or excipients of any of the trial drugs
- Use of any investigational drug within 4 weeks of randomization (unless a longer period is required by local regulations)

EGFR = epidermal growth factor receptor; RECIST = Response Evaluation Criteria In Solid Tumors; ECOG = Eastern Cooperative Oncology Group; ICH–GCP = International Conference on Harmonization–Good Clinical Practice; NSCLC = non-small cell lung cancer; CTC = Common Terminology Criteria; HIV = human immunodeficiency virus

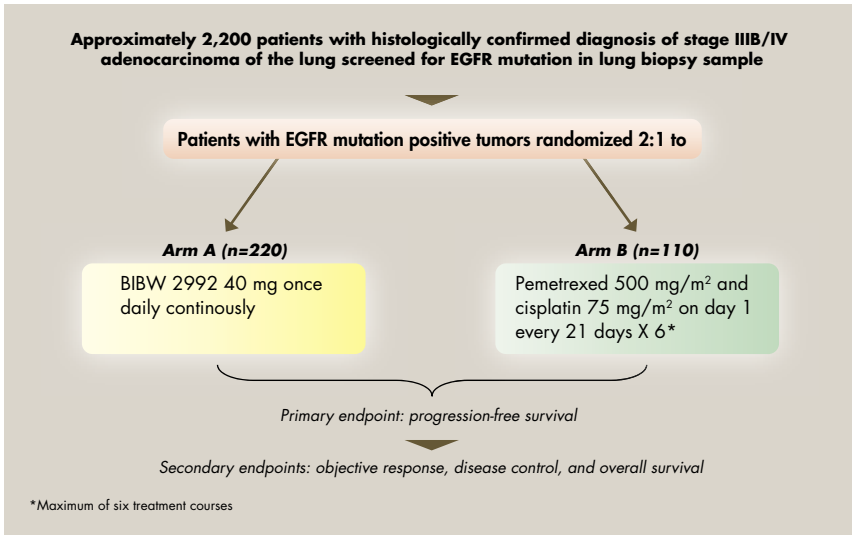

FIGURE 1 Treatment schema for LUX-Lung 3 trial

occurs. The safety of BIBW 2992 will be evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.

How can community oncologists enroll patients in the LUX-Lung 3 trial?

The LUX-Lung 3 trial is ongoing and actively recruiting eligible patients. For additional information about the trial and how to enroll patients, oncologists may:

- Review a complete description of the trial and a list of study locations at the National Institutes of Health Web site (www.clinicaltrials.gov/ct2/show/NCT00949650).
- Contact the Boehringer-Ingelheim Study Coordinator and ask about the LUX-Lung 3 trial.
  Phone: 800-243-0127
  E-mail: clintriage.rdg@boehringer-ingelheim.com

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Conflicts of interest: Dr. Sequist and Dr. Yang have received research funding for this trial from Boehringer Ingelheim Pharmaceuticals, Inc.