Quality of Life Analyses from the Randomized, Open-Label, Phase III PointBreak Study of Pemetrexed-Carboplatin-Bevacizumab followed by Maintenance Pemetrexed-Bevacizumab Versus Paclitaxel-Carboplatin-Bevacizumab followed by Maintenance Bevacizumab in Patients with Stage IIIB or IV Nonsquamous Non–Small-Cell Lung Cancer

*David R. Spigel, MD,[*] Jyoti D. Patel, MD,[†] Craig H. Reynolds, MD,[‡] Edward B. Garon, MD,[§] Robert C. Hermann, MD,[‖] Ramaswamy Govindan, MD,[¶] Mark R. Olsen, MD, PhD,[#] Katherine B. Winfree, PhD,[*]** Jian Chen, PhD,[*]** Jingyi Liu, PhD,[*]** Susan C. Guba, MD,[*]** Mark A. Socinski, MD,[†]†† and Philip Bonomi, MD[‡‡]*

Introduction: Treatment impact on quality of life (QoL) informs treatment management decisions in advanced nonsquamous non–small-cell lung cancer (NS NSCLC). QoL outcomes from the phase III PointBreak trial are reported.

Methods: Chemonaive patients (n = 939) with stage IIIB/IV nonsquamous non–small-cell lung cancer and Eastern Cooperative Oncology Group performance status 0 to 1 were randomized (1:1) to pemetrexed-carboplatin-bevacizumab (pemetrexed arm) or paclitaxel-carboplatin-bevacizumab (paclitaxel arm). Patients without progressive disease received maintenance pemetrexed-bevacizumab (pemetrexed arm) or bevacizumab (paclitaxel arm). QoL was assessed using Functional Assessment of Cancer Therapy (FACT)-General (FACT-G), FACT-Lung (FACT-L), and FACT/Gynecologic Oncology Group-Neurotoxicity (FACT-Ntx) instruments. Subscale scores, total scores, and trial outcome indices were analyzed using linear mixed-effects models. Post hoc analyses examined the association between baseline FACT scores and overall survival (OS).

Results: Mean score differences in change from baseline significantly favored the pemetrexed arm for the neurotoxicity subscale score, FACT-Ntx total scores, and FACT-Ntx trial outcome index. They occurred at cycle 2 ($p < 0.001$) and persisted through induction cycles 2 to 4 and six maintenance cycles. Investigator-assessed, qualitative, drug-related differences in grade 2 (1.6% versus 10.6%) and grade 3 (0.0% versus 4.1%) sensory neuropathy and grade 3/4 fatigue (10.9% versus 5.0%, $p = 0.0012$) were observed between the pemetrexed and paclitaxel arms. Baseline FACT-G, FACT-L, and FACT-Ntx scores were significant prognostic factors for OS ($p < 0.001$).

Conclusions: Randomized patients reported similar changes in QoL, except for less change from baseline in neurotoxicity on the

*Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN; †Feinberg School of Medicine, Northwestern University, Chicago, IL; ‡Ocala Oncology, Ocala, FL and US Oncology Research, Inc., Houston, TX; §David Geffen School of Medicine at UCLA/Translational Research in Oncology-US, Los Angeles, CA; ‖Northwest Georgia Oncology Centers, Marietta, GA; ¶Washington University School of Medicine, St. Louis, MO; #Tulsa Cancer Institute, Tulsa, OK; **Eli Lilly and Company, Indianapolis, IN; ††University of Pittsburgh Cancer Institute, University of Pittsburgh, Pittsburgh, PA; and ‡‡Rush University Medical Center, Chicago, IL.

Clinical trial registration: **Clinical Trial Registry ID:** NCT00762034

Presented, in part, at the American Society of Clinical Oncology Quality Care Symposium, San Diego

This study was sponsored by Eli Lilly and Company and Genentech/Roche.

Disclosure: D.R.S. has received consulting fees or honorarium and support from Eli Lilly for travel to meetings for this study. C.R. receives consulting fees or honorarium from Eli Lilly and has received support from Eli Lilly for travel to a meeting for this study. He has received ongoing payment for lectures including service on speakers bureaus from Eli Lilly. He has been a member of the speakers bureaus for and has performed advisory board work with Eli Lilly and Genentech. His employing organization receives grant funding from Eli Lilly. E.B.G. has received support from Eli Lilly for travel to an investigator meeting. His employing organization receives grant funding from Eli Lilly for a clinical trial. His employing organization has received payment for consultancy from Boehringer Ingelheim and has an ongoing relationship with Pfizer, AstraZeneca, Novartis Genentech, and Puma Biotechnology. He has also received funding from the National Institutes of Health for research on which this article is based. R.C.H.'s employing organization receives payment of direct expenses incurred in conduct of the clinical trial per the sponsor agreement. He receives payment from Genentech/Roche for lectures related to a different product than in this study. R.G. is a consultant for and receives funding from Pfizer, Genentech/Roche, Bristol-Myers Squibb, Merck, Boehringer Ingelheim, Abbott Oncology, Covidien, and Mallinckrodt. K.B.W. and J.C. are employees of Eli Lilly with stock/stock options. J.L. is an employee of Eli Lilly. S.C.G. is an employee of Eli Lilly with stock/stock options, and the company has paid for travel, accommodations, and meeting expenses. M.A.S. is an consultant for and receives funding from Celgene and Teva. He receives grant funding from Genentech, GlaxoSmithKline, Merrimack, and Signa. P.B.'s employing organization has received grant funding from Eli Lilly. For the remaining authors, no conflicts of interests were declared.

DOI: 10.1097/JTO.0000000000000277.

ISSN: 1556-0864/15/1002-0353

Address for correspondence: David R. Spigel, MD, 250 25th Avenue North, Suite 100 Nashville, TN 37203. E-mail: dspigel@tnonc.com

pemetrexed arm; investigators reported greater neurotoxicity on the paclitaxel arm and greater fatigue on the pemetrexed arm. Higher baseline FACT scores were favorable prognostic factors for OS.

Key Words: Nonsquamous non–small-cell lung cancer, Pemetrexed, Bevacizumab, Functional assessment of cancer therapy, Paclitaxel.

(*J Thorac Oncol.* 2015;10: 353–359)

Before and throughout the course of treatment, patients with non–small-cell lung cancer (NSCLC) experience problematic symptoms associated with their disease, which adversely affect their functional status and quality of life (QoL).[1,2] Many patients with advanced disease do not have curative treatment options, and therefore, they seek prolongation of survival without negatively impacting QoL.[3] To assess patient-reported outcomes, physicians may administer questionnaires to patients to measure activities of daily living, symptoms, disease-specific or general QoL, or physicians may simply ask comparable symptom- or QoL-related questions during their clinical assessment of the patient. Interest in these patient-reported outcomes has increased as new therapies and combination treatments are investigated, many of which have similar efficacies; this interest has underscored the importance of measuring patient-reported outcomes in clinical trials along with traditional end points, such as tumor response and survival. As part of this study, we present patients' reports of their experience on treatment by assessment of QoL utilizing specific, validated patient reported outcome assessments. Information gained from patients may add substantial insight into the patient experience and may guide decision making for the selection of appropriate therapies for a given patient.

In addition to guiding treatment decision making based on patient-experienced toxicities, the Functional Assessment of Cancer Therapy-Lung (FACT-L) instrument has been used previously to predict efficacy outcomes for patients more likely to respond to treatment.[4] For example, the baseline FACT-General (FACT-G) total score (TS) has been shown to be a statistically significant predictor of survival in patients with advanced lung cancer.[5]

The phase III PointBreak study, previously reported,[6] compared pemetrexed-carboplatin-bevacizumab followed by pemetrexed-bevacizumab (pemetrexed arm) with paclitaxel-carboplatin-bevacizumab followed by bevacizumab (paclitaxel arm) for first-line and maintenance treatment of patients with advanced nonsquamous NSCLC. The primary end point of superior overall survival (OS) for the pemetrexed arm was not met: 12.6 (pemetrexed arm) versus 13.4 months (paclitaxel arm); hazard ratio 1.00; $p = 0.949$.[6] The secondary efficacy end point of progression-free survival was superior for the pemetrexed arm compared with the paclitaxel arm (6.0 versus 5.6 months; hazard ratio 0.83; $p = 0.012$). Both regimens demonstrated tolerability; however, the toxicity profiles differed. An additional secondary end point focused on QoL and on evaluating differences in patient-reported outcomes, as assessed by the FACT-G, FACT-L, and FACT/Gynecologic Oncology Group-Neurotoxicity (FACT-Ntx) instruments; these results are presented here as are investigator-reported toxicity scores and associated resource use. Post hoc analyses that examined prognostic factors for OS are also reported.

PATIENTS AND METHODS

Patients

This study included patients with stage IIIB or IV advanced nonsquamous NSCLC[7] who had no prior systemic therapy for lung cancer and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; patients with stable-treated brain metastases were permitted to participate in the study. PointBreak was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was approved by each participating center's ethics review board. All patients provided informed consent before receiving treatment for inclusion in the study and to comply with the Declaration of Helsinki.[6]

Treatment

Treatment consisted of up to four cycles of induction therapy and for patients with at least stable disease was followed by maintenance therapy until disease progression or treatment discontinuation. Using the same dosing regimens for bevacizumab as in ECOG study E4599,[8] eligible patients were randomized (1:1 ratio) to either the experimental arm (pemetrexed arm) or the control arm (paclitaxel arm). The experimental arm included intravenous (IV) pemetrexed (Alimta, Eli Lilly and Company, Indianapolis, IN) 500 mg/m^2 + carboplatin (Paraplatin, Bristol-Myers Squibb, New York, NY) area under the curve 6 + bevacizumab (Avastin, Genentech, South San Francisco, CA) 15 mg/kg on day 1 of up to four 21-day cycles, followed by IV pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg for maintenance; while the control arm included IV paclitaxel (Taxol, Bristol-Myers Squibb) 200 mg/m^2 + carboplatin area under the curve 6 + bevacizumab 15 mg/kg on day 1 of up to four 21-day cycles, followed by IV bevacizumab 15 mg/kg for maintenance. Randomization occurred before induction therapy, and patients were stratified according to disease stage (IIIB versus IV), ECOG PS (0 versus 1), sex (male versus female), and measurable versus nonmeasurable disease. Patients randomized to the pemetrexed arm received folic acid, vitamin B12 supplementation, and premedication per the pemetrexed label[9]; patients randomized to the paclitaxel arm also received premedication per the paclitaxel label.[10] Concomitant supportive therapies, such as erythropoietic agents or granulocyte colony-stimulating factors, were allowed according to the American Society of Clinical Oncology[11] and National Comprehensive Cancer Network[12] guidelines. After four cycles of induction treatment, patients with a complete response, partial response, or stable disease, per Response Evaluation Criteria in Solid Tumors 1.0,[13] received the specified maintenance therapy. Patients experiencing protocol-specified adverse events had dose reductions or drug discontinuations.[1]

Toxicity and Patient-Reported FACT Assessments

Toxicity analyses included all patients who received at least one dose of a study drug. Toxicity was

