- July 7, 2011). Bethesda, MD: ClinicalTrials.gov; [received September 20, 2007; updated October 4, 2011]. Available from: <http://clinicaltrials.gov/ct2/show/NCT00533949?term=NCT00533949&rank=1>
25. Stereotactic body radio therapy (SBRT) for early-stage non-small cell lung cancer (NSCLC) (SBRT-NSCLC) (accessed July 7, 2011). Bethesda, MD: ClinicalTrials.gov; [received March 25, 2009; updated July 12, 2011]. Available from: <http://clinicaltrials.gov/ct2/show/NCT00870116?term=NCT00870116&rank=1>
 26. Randomized study to compare cyberknife to surgical resection in stage I non-small cell lung cancer (STARS) (accessed July 7, 2011). Bethesda, MD: ClinicalTrials.gov; [received February 7, 2009; updated October 3, 2011]. Available from: <http://clinicaltrials.gov/ct2/show/NCT00840749?term=NCT00840749&rank=1>
 27. van Loon J, Offermann C, Ollers M, van Elmpt W, Vegt E, Rahmy A, Dingemans AM, Lambin P, De Ruyscher D. Early CT and FDG-metabolic tumour volume changes show a significant correlation with survival in stage I-III small cell lung cancer: a hypothesis generating study. *Radiother Oncol* 2011;99:172-175.
 28. Bentzen SM. Theragnostic imaging for radiation oncology: dose-painting by numbers. *Lancet Oncol* 2005;6:112-117.
 29. Cox J: Proton beam therapy vs. intensity modulated radiation therapy for locally advanced non-small cell lung cancer, IASCL Proceedings, Session MO02.12, 2011.
 30. Kim ES, Herbst RS, Wistuba II, Lee JJ, Blumenschein GR, Tsao A, Stewart DJ, Hicks ME, Erasmus J, Gupta S, *et al.* The BATTLE trial: personalizing therapy for lung cancer. *Ca Discovery* 2011;1: 44-53.

Copyright © 2011 by the American Thoracic Society

DOI: 10.1164/rccm.201107-1264ED

Con: The Case for Expanded Lung Cancer Research Support

Lung cancer embodies a devastating disease with an overall 5-year survival rate of patients with metastatic disease remaining less than 15%. Importantly, lung cancer represents the leading cause of cancer-related deaths in the United States, accounting for 30% of all male cancer deaths and 26% of all female cancer deaths (1). Despite these disturbing numbers, emerging data suggest that considerable progress has been made in the treatment of selected groups of patients with lung cancer. These results represent astonishing leaps in the use of targeted therapies for lung cancer. We believe that, given the recent advances in targeted lung cancer treatment, augmented research support would rapidly translate into better patient outcomes.

One of the major signals that improved care for patients with lung cancer can augment outcomes for these patients can be discerned from an article describing the disparity in lung cancer practices and outcomes (2). In this important work, the investigators demonstrate that patients who lack insurance or Medicaid benefits consistently had worse outcomes than other patients with a diagnosis of lung cancer. This disparity in insurance status demonstrates important findings, including higher incidence of lung cancer, worse stage at diagnosis, and poorer survival even after adjustment for the stage of diagnosis. A simple nihilistic approach to lung cancer would strongly argue that, because treatments may have limited efficacy, overall earlier diagnosis or the institution of aggressive treatments would have no change in patient outcomes. The work by Slatore and colleagues illustrates that improvements in access of care would immediately lead to improvements in patient outcomes for those with lung cancer.

A second degree of evidence for the importance of specialized services for lung cancer patients is provided in the work by Onega and coworkers (3). In this study, the investigators were particularly interested in outcomes for patients with either lung, breast, colorectal, or prostate cancer at National Cancer Institute (NCI)-designated cancer centers. In their retrospective analysis, all patients treated in NCI-designated cancer centers for these four common cancers were assessed for overall survival. The investigators conclude that there is a decreased likelihood of cancer-specific mortality at 1 year for all four types of cancer examined when these patients receive care at NCI-designated cancer centers. For the 3-year cancer-specific mortality, only lung cancer maintains an odds ratio significantly less than 1.0; and therefore, the benefit of treatment for this highly difficult illness appears to be improved at centers with the optimum access to research and

experimental therapeutics. There are several potential reasons for the survival benefits of patients treated at NCI-designated cancer centers. This benefit may be related to processes of care, such as receipt of surgery, guideline-based treatment, and multidisciplinary care teams. Furthermore, access to cutting-edge therapeutic trials is, at times, restricted to NCI-designated cancer centers.

One major emphasis on current cancer therapies involves the investigation and utilization of targeted therapies. The overall theory implies that carcinogenesis may result from specific “driver” mutations. Targeting these specific “driver” mutations is viewed as the most optimal way to personalize and rationalize selected treatment approaches for cancers—in particular lung cancer. Certainly one of the premier examples of this strategy and approach occurs with chronic myelogenous leukemia (CML). The advent of a successful targeted therapy for CML demonstrated the high utility of a single driver mutation in an oncologic process (4). Moreover, the definition of resistance mutations and the forward targeting for these mutations changed the paradigm of how cancer treatment should proceed (5). The expansion of this approach to other tumors, in particular into solid tumor biology, has led to accelerated advances in lung cancer treatment.

It has been known for quite some time that one driver for lung cancer is signaling through the epidermal growth factor receptor (EGFR). Adequate targeting of this tyrosine kinase (TK) had been a goal of several pharmaceutical companies. First-generation anti-EGFR therapies were developed in the 1990s and were all directed against wild-type EGFR receptor, which was demonstrated to be overexpressed on numerous epithelial cancer types. Therapeutic agents included the small molecule tyrosine kinase inhibitors (TKIs) such as gefitinib (Iressa; AstraZeneca, Wilmington, DE) and erlotinib (Tarceva; Genentech/OSI Pharmaceuticals, Farmingdale, NY) and the EGFR-specific antibodies cetuximab (Erbix; ImClone/Merck/Bristol-Myers Squibb, Branchburg, NJ). During the initial investigation of this class of compounds, researchers noted a small subgroup of patients having extraordinary response rates (6). Moreover, in 2004 molecular analysis revealed that mutant EGFR conveyed susceptibility to treatment with EGFR inhibitors (7-9). Since that time, a significant advancement has been made in rational, biologically based treatment for patients with EGFR mutant non-small cell lung cancer (NSCLC). Various forms of mutations in the EGFR TK have been described. In addition, more recent third-generation EGFR TKIs are in development. Combinatorial treatment is being undertaken to target alternative pathways that are activated in the setting of acquired resistance in

Figure 1. U.S. cancer deaths versus federal research funding per death. Data for 2009 demonstrate that lung cancer has the lowest research funding per cancer death compared with next three deadliest cancers: colorectal, breast, and prostate. Reprinted by permission from Reference 17. Estimated deaths by cancer type in the U.S. for 2009 are from the American Cancer Society Facts and Figures, 2009: <http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-figures-2009>. Annual funding figures represent the National Cancer Institute (NCI) and Department of Defense estimated 2009 spending*: NCI: <http://budgettool.cancer.gov/budget-spending/funding-by-cancer-type/fiscal-year-2009.aspx>. Department of Defense Lung, Breast, and Prostate Research Program descriptions available at <http://cdmrp.army.mil/researchprograms.shtml>.

* While the Centers for Disease Control & Prevention (CDC) also funds cancer research, a breakdown of spending between research and public health interventions is not currently available.

EGFR mutant NSCLC. These discoveries define a paradigm that will be utilized in the future for lung cancer treatment and represent the first significant advance in lung cancer treatment in several decades.

More recently, the discovery of anaplastic lymphoma kinase (ALK) inhibition as a potential target for NSCLC has proceeded from discovery to novel targeted treatment within a significantly shorter period of time than many other cancer treatment advances (10). In effect, the first description of rearrangements of the ALK gene in an NSCLC was reported in 2001 (11). ALK encodes for a tyrosine kinase normally expressed only in selected neuronal cells. In a rare subset of NSCLC, an interstitial deletion and inversion within chromosome 2p results in fusion of the end terminal portion of the protein encoded by the echinoderm microtubule-associated protein-like4 (EML4) gene with the intracellular signaling portion of the ALK receptor tyrosine kinase (11). Due to the fact that ALK inhibition had been previously perceived as a rational drug target by selected pharmaceutical corporations, the rapid clinical development of ALK-targeted therapy was greatly accelerated (12, 13). Therefore, scientists were positioned to investigate the pathogenic mechanism of EML4-ALK in NSCLC pathogenesis. Moreover, potential treatment with crizotinib (an ALK inhibitor) could be envisioned as a clinical target. Administration of specific inhibitors of the ALK-tyrosine kinase activity resulted in rapid eradication of nodules in a pre-clinical animal model of this tumor (14). In 2008, a Phase-I clinical trial was initiated, followed rapidly by reports of cases with dramatic clinical benefit of ALK-targeted therapy among patients with ALK-positive NSCLC (15). Ultimately, in 2010, a Phase-III trial for targeted treatment with crizotinib was undertaken, and positive results have led to one of the most rapid translations of biologic discovery into targeted therapy (15). Utilizing the now “tried and true” paradigm of acquired resistance, investigators were also able to report the discovery of two secondary mutations within the kinase domain of EML4-ALK in tumor cells isolated from a patient during the relapse phase of treatment with an ALK inhibitor (16).

In conclusion, we have a long way to go to defeat lung cancer. Currently, lung cancer remains significantly underfunded in comparison to other cancers on a per-patient-death basis. The National Lung Cancer Partnership estimates that, for 2009, lung

cancer federal funding (including NIH and the Department of Defense) per cancer death was lower than that of colorectal, breast, or prostate cancers (Figure 1). Phenomenal advances have been made in the concept of targeted therapies with clinical implications for finding driver mutations in lung cancer. Improved care leads to better outcomes for lung cancer, both in terms of access to care and health disparities, as well as treatment at NCI-designated cancer centers. Moreover, we have strong evidence that finding biologically relevant driver mutations, and targeting these mutations with chemotherapy, can improve outcomes. Indeed, the overall survival rate for lung cancer has improved from 7 months in 1976 to 32 months in 2009 (6). We are only beginning our assault on lung cancer. There are numerous research frontiers requiring augmented funding, including targeted therapies for lung cancer, personalized treatment for lung cancer, and early detection and chemoprevention. Aggressive investigation is highly likely to improve outcomes in this devastating disease.

Author disclosures are available with the text of this article at www.atsjournals.org.

MARK W. GERACI, M.D.

*Division of Pulmonary Sciences and Critical Care Medicine
University of Colorado Denver
Denver, Colorado*

ROBERT L. KEITH, M.D.

*Division of Pulmonary Sciences and Critical Care Medicine
University of Colorado Denver
Denver, Colorado*

and

*VA Eastern Colorado Health Care System
Denver, Colorado*

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer Statistics, 2009. *CA Cancer J Clin* 2009;59:225–249.
2. Slatore CG, Au DH, Gould MK. An Official American Thoracic Society Systematic Review: Insurance status and disparities in lung cancer practices and outcomes. *Am J Respir Crit Care Med* 2010;182:1195–1205.
3. Onega T, Duell EJ, Shi X, Demidenko E, Gottlieb D, Goodman DC. Influence of NCI Cancer Center attendance on mortality in lung, breast, colorectal, and prostate cancer patients. *Med Care Res Rev* 2009;66:542–560.

4. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, *et al.* Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001;344:1031–1037.
5. Sawyers CL. Even better kinase inhibitors for chronic myeloid leukemia. *N Engl J Med* 2010;362:2314–2315.
6. Pao W, Chmielecki J. Rational, biologically based treatment of egfr-mutant non-small-cell lung cancer. *Nat Rev Cancer* 2010;10:760–774.
7. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129–2139.
8. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497–1500.
9. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, Singh B, Heelan R, Rusch V, Fulton L, *et al.* EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA* 2004;101:13306–13311.
10. Gerber DE, Minna JD. ALK inhibition for non-small cell lung cancer: from discovery to therapy in record time. *Cancer Cell* 2010;18: 548–551.
11. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara S, Watanabe H, Kurashina K, Hatanaka H, *et al.* Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007;448:561–566.
12. Christensen JG, Zou HY, Arango ME, Li Q, Lee JH, McDonnell SR, Yamazaki S, Alton GR, Mroczkowski B, Los G. Cyto-reductive anti-tumor activity of pf-2341066, a novel inhibitor of anaplastic lymphoma kinase and C-Met, in experimental models of anaplastic large-cell lymphoma. *Mol Cancer Ther* 2007;6:3314–3322.
13. Zou HY, Li Q, Lee JH, Arango ME, McDonnell SR, Yamazaki S, Koudriakova TB, Alton G, Cui JJ, Kung PP, *et al.* An orally available small-molecule inhibitor of C-Met, PF-2341066, exhibits cyto-reductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. *Cancer Res* 2007;67:4408–4417.
14. Soda M, Takada S, Takeuchi K, Choi YL, Enomoto M, Ueno T, Haruta H, Hamada T, Yamashita Y, Ishikawa Y, *et al.* A mouse model for EML4-ALK-positive lung cancer. *Proc Natl Acad Sci USA* 2008;105: 19893–19897.
15. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, Ou SH, Dezube BJ, Janne PA, Costa DB, *et al.* Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010; 363:1693–1703.
16. Choi YL, Soda M, Yamashita Y, Ueno T, Takashima J, Nakajima T, Yatabe Y, Takeuchi K, Hamada T, Haruta H, *et al.* EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. *N Engl J Med* 2010;363:1734–1739.
17. National Lung Cancer Partnership. Lung Cancer Facts—Lung Cancer Research (accessed June 3, 2011). Available from: <http://www.nationallungcancerpartnership.org/lung-cancer-info/lung-cancer-research>

Published 2011 by the American Thoracic Society
DOI: 10.1164/rccm.201104-0697ED