AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** James L. Rubenstein, Up To Date; Lawrence D. Kaplan, Up To Date **Research Funding:** James L. Rubenstein, Genentech, Celgene **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

REFERENCES

1. Glantz MJ, Cole BF, Recht L, et al: High-dose intravenous methotrexate for patients with nonleukemic leptomeningeal cancer: Is intrathecal chemotherapy necessary? J Clin Oncol 16:1561-1567, 1998

2. Batchelor T, Carson K, O'Neill A, et al: Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: A report of NABTT 96-07. J Clin Oncol 21:1044-1049, 2003

3. Rubenstein JL, Combs D, Rosenberg J, et al: Rituximab therapy for CNS lymphomas: Targeting the leptomeningeal compartment. Blood 101:466-468, 2003

4. Rubenstein JL, Fridlyand J, Abrey L, et al: Phase I study of intraventricular administration of rituximab in patients with recurrent CNS and intraocular lymphoma. J Clin Oncol 25:1350-1356, 2007

5. Batchelor TT, Grossman SA, Mikkelsen T, et al: Rituximab monotherapy for patients with recurrent primary CNS lymphoma. Neurology 76:929-930, 2011

6. Kadoch C, Li J, Wong VS, et al: Complement activation and intraventricular rituximab distribution in recurrent central nervous system lymphoma. Clin Cancer Res [epub ahead of print on November 7, 2013]

7. Reni M, Mason W, Zaja F, et al: Salvage chemotherapy with temozolomide in primary CNS lymphomas: Preliminary results of a phase II trial. Eur J Cancer 40:1682-1688, 2004

8. Reni M, Zaja F, Mason W, et al: Temozolomide as salvage treatment in primary brain lymphomas. Br J Cancer 96:864-867, 2007

9. Osoba D, Brada M, Yung WK, et al: Health-related quality of life in patients treated with temozolomide versus procarbazine for recurrent glioblastoma multiforme. J Clin Oncol 18:1481-1491, 2000

10. Ott RJ, Brada M, Flower MA, et al: Measurements of blood-brain barrier permeability in patients undergoing radiotherapy and chemotherapy for primary cerebral lymphoma. Eur J Cancer 27:1356-1361, 1991

11. Rubenstein JL, Fridlyand J, Shen A, et al: Gene expression and angiotropism in primary CNS lymphoma. Blood 107:3716-3723, 2006

12. Soussain C, Suzan F, Hoang-Xuan K, et al: Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. J Clin Oncol 19:742-749, 2001

13. Wieduwilt MJ, Valles F, Issa S, et al: Immunochemotherapy with intensive consolidation for primary CNS lymphoma: A pilot study and prognostic assessment by diffusion-weighted MRI. Clin Cancer Res 18:1146-1155, 2012

14. Ferreri AJ, Reni M, Foppoli M, et al: High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: A randomised phase 2 trial. Lancet 374:1512-1520, 2009

15. Relling MV, Mahmoud HH, Pui CH, et al: Etoposide achieves potentially cytotoxic concentrations in CSF of children with acute lymphoblastic leukemia. J Clin Oncol 14:399-404, 1996

16. Boehme V, Zeynalova S, Kloess M, et al: Incidence and risk factors of central nervous system recurrence in aggressive lymphoma: A survey of 1693 patients treated in protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Ann Oncol 18:149-157, 2007

17. Batchelor TT: Flying solo: Chemotherapy without radiation for primary CNS lymphoma. J Clin Oncol 31:3051-3053, 2013

18. Morris PG, Correa DD, Yahalom J, et al: Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: Final results and long-term outcome. J Clin Oncol 31:3971-3979, 2013

19. Sun A, Bae K, Gore EM, et al: Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: Neurocognitive and quality-of-life analysis. J Clin Oncol 29:279-286, 2011

20. Mizumatsu S, Monje ML, Morhardt DR, et al: Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. Cancer Res 63:4021-4027, 2003

21. Monje ML, Mizumatsu S, Fike JR, et al: Irradiation induces neural precursor-cell dysfunction. Nat Med 8:955-962, 2002

22. Relling MV, Rubnitz JE, Rivera GK, et al: High incidence of secondary brain tumours after radiotherapy and antimetabolites. Lancet 354:34-39, 1999

23. Walter AW, Hancock ML, Pui CH, et al: Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. J Clin Oncol 16:3761-3767, 1998

24. Chamberlain MC: Should dose-intense immnochemotherapy be the new standard of care for primary CNS lymphoma? J Clin Oncol 32:857-858, 2014

25. Rubenstein JL, Hsi ED, Johnson JL, et al: Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). J Clin Oncol 31:3061-3068, 2013

26. Rubenstein JL, Gupta NK, Mannis GN, et al: How I treat CNS lymphomas. Blood 122:2318-2330, 2013

27. Damon L, Damon LE, Gaensler K, et al: Impact of intensive PBSC mobilization therapy on outcomes following auto-SCT for non-Hodgkin's lymphoma. Bone Marrow Transplant 42:649-657, 2008

28. Damon LE, Johnson JL, Niedzwiecki D, et al: Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909. J Clin Oncol 27:6101-6108, 2009

29. Schaich M, Parmentier S, Kramer M, et al: High-dose cytarabine consolidation with or without additional amsacrine and mitoxantrone in acute myeloid leukemia: Results of the prospective randomized AML2003 trial. J Clin Oncol 31:2094-2102, 2013

30. Schaich M, Röllig C, Soucek S, et al: Cytarabine dose of 36 g/m^2 compared with 12 g/m^2 within first consolidation in acute myeloid leukemia: Results of patients enrolled onto the prospective randomized AML96 study. J Clin Oncol 29:2696-2702, 2011

31. Linker CA, Owzar K, Powell B, et al: Auto-SCT for AML in second remission: CALGB study 9620. Bone Marrow Transplant 44:353-359, 2009

32. Ponzoni M, Issa S, Batchelor TT, et al: Beyond high-dose methotrexate and brain radiotherapy: Novel targets and agents for primary CNS lymphoma. Ann Oncol [epub ahead of print on November 30, 2013]

DOI: 10.1200/JCO.2013.53.8942; published online ahead of print at www.jco.org on February 3, 2014

Do We Really Need Another Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor in First-Line Treatment for Patients With Non–Small-Cell Lung Cancer and *EGFR* Mutations?

To the Editor: Sequist et al[1] recently published in *Journal of Clinical Oncology* the results of a phase III study comparing afatinib to standard first-line chemotherapy in patients with metastatic lung adenocarcinoma with *EGFR* mutations.

Since 2004, when *EGFR* became a target,[2-4] three similar molecules have been studied and developed for the same indication. So far, three drugs (gefitinib, erlotinib, and afatinib) have been approved as first-line treatment in a population representing approximately 10% of patients with non–small-cell lung cancer (NSCLC). Furthermore, to our knowledge, at least one other drug[5] is under investigation for the same population.

The regulatory agencies accepted the commercialization of a third drug without any direct comparison with the other two already-marketed drugs in such a small subset of patients. Nevertheless, we need to understand how afatinib could possibly be implemented in clinical practice. At the date the LUX-Lung 3 trial was started, data on IPASS were already known, and gefitinib was already considered standard first-line treatment for *EGFR*-mutated patients, as was erlotinib later on.

Table 1. Randomized Phase III Trials Comparing Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor and Standard Chemotherapy as First-Line Treatment in Patients With Non–Small-Cell Lung Cancer: Results in *EGFR*-Mutated Patients and According to Different Variants

Trial	No. of Patients	RR (%)	*P*	PFS (months)	HR (95% CI)	*P*	PFS HR (95% CI)					
							No. of Patients	Del19	No. of Pts	L858R	No. of Patients	Others
IPASS[8,9] (N = 261)												
Gefitinib 250 mg daily	132	71.2	<.001	9.5	0.48 (0.36 to 0.64)	<.001	66	0.38 (0.26 to 0.56)	64	0.55 (0.35 to 0.87)	3	NA
CBDCA AUC 5-6 + paclitaxel 200 mg/m^2 every 21 d	129	47.3		6.3			74		47		7	
FIRST-SIGNAL[10] (N = 42)												
Gefitinib 250 mg daily	26	84.6	.002	8.0	0.54 (0.27 to 1.10)	.086				NA		
CDDP 80 mg/m^2 d 1 + gemcitabine 1,250 mg/m^2 d 1, d 8 every 21 d	16	37.5		6.3								
WJTOG3405[11] (N = 177)												
Gefitinib 250 mg daily	88	62.1	<.001	9.2	0.49 (0.34 to 0.71)	<.001	50	0.45 (0.27 to 0.77)	36	0.51 (0.29 to 0.90)	—	—
CDDP 80 mg/m^2 d 1 + docetaxel 60 mg/m^2 d 1 every 21 d	89	32.2		6.3			37		49			
NEJSG002[12] (N = 228)												
Gefitinib 250 mg daily	114	73.7	<.001	10.8	0.30 (0.22 to 0.41)	<.001				NA		
CBDCA AUC 6 d 1 + paclitaxel 200 mg/m^2 d 1 every 21 d	114	30.7		5.4								
OPTIMAL[13] (N = 154)												
Erlotinib 150 mg daily	82	83	<.001	13.7	0.16 (0.11 to 0.26)	<.001	43	0.13 (0.07 to 0.25)	39	0.26 (0.14 to 0.49)	—	—
CBDCA AUC 5 d 1 + gemcitabine 1,000 mg/m^2 d 1, d 8 every 21 d	72	36		4.6			39		33			
EURTAC[14] (n = 173)												
Erlotinib 150 mg daily	86	64	<.001	9.7	0.37 (0.25 to 0.54)	<.001	57	0.30 (0.18 to 0.50)	29	0.55 (0.29 to 1.02)	—	—
Different CT regimens	87	18		5.2			58		29			
TORCH[15] (N = 39)												
Erlotinib 150 mg daily → CDDP + gemcitabine	19	42.1	NA	9.7	0.60 (0.30 to 1.20)	.006				NA		
CDDP + gemcitabine → erlotinib 150 mg daily	20	25.0		6.9								
LUX-Lung 3[1] (N = 345) (independent assessment)												
Afatinib 40 mg daily	230	56	.001	11.1	0.58 (0.43 to 0.78)	.001	113	0.28 (0.18 to 0.44)	91	0.73 (0.46 to 1.17)	26	NA
CDDP 75 mg/m^2 d 1 + pemetrexed 500 mg/m^2 d 1 every 21 d	115	23		6.9			57		47		11	
LUX-Lung 6[16] (N = 364) (independent assessment)												
Afatinib 40 mg daily	242	67	NA	11.0	0.28 (0.20 to 0.39)	<.001	186	0.20 (0.13 to 0.33)	138	0.32 (0.19 to 0.52)	40	0.55 (0.22 to 1.43)
CDDP 75 mg/m^2 d 1 + gemcitabine 1,000 mg/m^2 d 1, d 8 every 21 d	122	23		5.6								

Abbreviations: AUC, area under the curve; CBDCA, carboplatin; CDDP, cisplatin; CT, chemotherapy; d, day; HR, hazard ratio; NA, not available; PFS, progression-free survival; RR, response rate.

Table 2. Toxicity in Randomized Phase II/III Trials Comparing Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor and Standard Chemotherapy in First-Line Treatment for Non–Small-Cell Lung Cancer

				Diarrhea				Rash				Paronychia			
		Global Toxicity %		All Grades		Grades 3-4		All grades		Grades 3-4		All grades		Grades 3-4	
Trial	No.	All Grades	Grades 3-4	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
IPASS[8]															
Gefitinib 250 mg daily	607	NA	28.7	283	46.6	29	4.9	402	66.2	19	3.1	82	13.5	2	0.3
CBDCA + paclitaxel once every 21 d	589	NA	61	128	21.7	8	1.4	132	22.4	5	0.8	0	0	0	0
FIRST-SIGNAL[10]															
Gefitinib 250 mg daily	159	NA	28.9	79	49.7	4	2.5	115	72.4	47	29.3	NA		NA	
CDDP + gemcitabine once every 21 d	150	NA	68	45	30	2	1.3	20	13.3	3	2	NA		NA	
WJTOG3405[11]															
Gefitinib 250 mg daily	87	NA	NA	47	54	1	1.1	74	85	2	2.3	28	32.2		1 1.2
CDDP - docetaxel	88	NA	NA	35	39.8	0	0	7	7.9	0	0	1	1.1	0	0
NEJSG002[12]															
Gefitinib 250 mg daily	114	94.7	41.2	39	34.2	1	0.9	81	71.1	6	5.3	11	9.6	3	2.6
CBDCA + paclitaxel once every 21 d	113	97.3	71.7	7	6.2	0	0	25	22.1	3	2.7	0	0	0	0
OPTIMAL[13]															
Erlotinib 150 mg daily	83	93	17	21	25	1	1	61	73	2	2	3	4	0	0
CBDCA - gemcitabine	72	96	65	4	6	0	0	14	19	0	0	0	0	0	0
EURTAC[14]															
Erlotinib 150 mg daily	84	98	45	48	57	4	5	67	80		11 13	NA		NA	
CDDP/CBDCA + docetaxel/gemcitabine	82	99	67	15	18	0	0	4	5		0	NA		NA	
TORCH[15]															
Erlotinib 150 mg daily	368	NA	NA	152	41	20	5.5	252	68	40	11	NA		NA	
CDDP - gemcitabine	372	NA	NA	91	25	2	1	135	37	26	7	NA		NA	
INVITE[17]															
Gefitinib 250 mg daily	94	83	41.5	24	25.5	4	4.3	23	24.5	2	2.1	NA		NA	
Vinorelbine	96	89.5	55.2	13	13.5	4	4.2	3	3.1	0	0	NA		NA	
Lilenbaum[18]															
Erlotinib 150 mg daily	52	85	27	23	44		3 6	34	65	4	8	NA		NA	
CBDCA - paclitaxel	51	98	41	10	20		0	3	6	0	0	NA		NA	
IFTC-0301[19]															
Gefitinib 250 mg daily	43	72	23	12	28	2	5	17	39	1	2	NA		NA	
Gemcitabine or docetaxel	42/42	73/78	29/56	5-6	12/15	0/1	2	1/7	2/16	0/2	4	NA		NA	
LUX-Lung 3[1]															
Afatinib 40 mg daily	229	100	1	218	95.2	33	14.4	204	89.1	37	16.2	130	56.8	26	11.4
CDDP - pemetrexed	111	98.2	5	17	15.3	0	0		7 6.3	0	0	0	0	0	0
LUX-Lung 6[16]															
Afatinib 40 mg daily	239	98.7	36		88.3		5.4		80.8		14.6		32.6	0	0
CDDP - gemcitabine	113	99.1	60.1		10.6	0	0		8.8	0	0	0	0	0	0

Abbreviations: CBDCA, carboplatin; NA, not available; CDDP, cisplatin.

An assumption was that afatinib was active in patients with rare mutations, and in particular for the T790M variant.[6-7] However, no confirmation data about the outcome of patients harboring T790M de novo or other rare mutations have been reported here.

In fact, Sequist et al[1] reported efficacy data only on the overall *EGFR*-mutated population and exon 19 and L858R variants, demonstrating a higher progression-free survival (PFS) and response rate (RR) compared with chemotherapy. These data merely confirm the results of clinical trials using erlotinib and gefitinib, without major differences in terms of PFS, neither in the overall population nor in patients with mutations in exon 19[1,8-16] (Table 1).

Furthermore, deep analysis of the toxicity data (Table 2) indicates the same common adverse effects of afatinib as reported with the other *EGFR* TKIs. However, the indirect comparison with the other phase III studies[8-19] shows an increase in diarrhea, rash, and nail disorders for this drug.

Moreover, in our opinion, the data on pharmacokinetics presented by Sequist et al[1] are not conclusive. In several studies including unselected patients with NSCLC treated with other EGFR TKIs, there seemed to be a direct correlation between the plasma dose levels, toxicity, and efficacy.[3,20-21] Sequist et al concluded that the pharmacokinetics, according to individual dose modification for toxicity, did not significantly influence the efficacy. Unfortunately, in this case the question whether higher plasma levels correlate with higher efficacy also remains unsolved.

The LUX-Lung 3 trial represents the only trial in patients with advanced *EGFR* mutation–positive NSCLC comparing an EGFR TKI to best-in class chemotherapy regimen in the first-line setting, and therefore its hazard ratio point estimate must be carefully interpreted when compared with those of the other drugs.

We are pleased that the results published met the primary end point, but it is difficult to understand how this new drug could possibly be implemented into clinical practice.

We still do not know which one—afatinib, erlotinib, or gefitinib—is the best option as first-line treatment in patients with *EGFR*-mutated NSCLC. In fact, as first-line therapy, the question of which is the best TKI will never be faced, as a direct comparison between erlotinib and gefitinib probably will never occur. So the question about the best first-line TKI will only partially be resolved when data of the ongoing LUX-Lung 7 and 8 trials are presented. Furthermore, after the publication of all these trials, the first developed drugs will probably lose their patent, creating competition in terms of cost. Presently, there are no data for second- or third-line treatments available for afatinib.

Research efforts are undertaken to develop new and similar drugs to treat a small subset of patients. However, it seems astounding that for such a niche therapeutic area, there are three similar drugs available, and that after nine phase III trials,[1,8-16] the question of whether one single drug is superior to the others is still unresolved. Furthermore, how to overcome acquired resistance and to treat patients after disease progression still remains unclear, and no drugs have been approved for post-progression treatment.

Unfortunately, as a result of a lack of direct comparisons made in the research carried out so far, prescriptive choice of EGFR TKIs will not presently be based on scientific evidence.

Eva R. Haspinger and Marina Chiara Garassino
Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy

Valter Torri and Michela Cinquini
Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

Filippo De Braud and Francesco Gelsomino
Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** Marina Chiara Garassino, Boehringer Ingelheim (U) **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

REFERENCES

1. Sequist LV, Yang JC, Yamamoto N, et al: Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with *EGFR* mutations. J Clin Oncol 31:3327-3334, 2013

2. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129-2139, 2004

3. Pérez-Soler R, Chachoua A, Hammond LA, et al: Determinants of tumor response and survival with erlotinib in patients with non–small-cell lung cancer. J Clin Oncol 22:3238-3247, 2004

4. Paez JG, Jänne PA, Lee JC, et al: EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 304:1497-1500, 2004

5. Kris M, Goldberg Z, Jänne PA, et al: Dacomitinib (PF-00299804), an irreversible pan-HER tyrosine kinase inhibitor (TKI), for first-line treatment of EGFR-mutant or HER2-mutant or -amplified lung cancers. Ann Oncol 23:400-446, 2012

6. Li D, Ambrogio L, Shimamura T, et al: BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene 27:4702-4711, 2008

7. Miller VA, Hirsh V, Cadranel J, et al: Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): A phase 2b/3 randomized trial. Lancet Oncol 13:528-538, 2012

8. Mok TS, Wu YL, Thongprasert S, et al: Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947-957, 2009

9. Fukuoka M, Wu YL, Thongprasert S, et al: Biomarker analyses and final overall survival results from a phase iii, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non–small-cell lung cancer in Asia (IPASS). J Clin Oncol 29:2866-2874, 2011

10. Han JY, Park K, Kim SW, et al: First-SIGNAL: First-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin Oncol 30:1122-1128, 2012

11. Mitsudomi T, Morita S, Yatabe Y, et al: Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. Lancet Oncol 11:121-128, 2010

12. Maemondo M, Inoue A, Kobayashi K, et al: Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. N Engl J Med 362:2380-2388, 2010

13. Zhou C, Wu YL, Chen G, et al: Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12:735-742, 2011

14. Rosell R, Carcereny E, Gervais R, et al: Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13:239-246, 2012

15. Gridelli C, Ciardiello F, Gallo C, et al: First-line erlotinib followed by second-line cisplatin- gemcitabine chemotherapy in advanced non–small-cell lung cancer: The TORCH randomized trial. J Clin Oncol 30:3002-3011, 2012

16. Wu YL, Zhou C, Hu CP, et al: LUX-Lung 6: A randomized, open-label, phase III study of afatinib vs gemcitabine/cisplatin as first-line treatment for Asian patients with EGFR mutation-positive advanced adenocarcinoma of the lung. J Clin Oncol 31:490s (suppl; abstr 8016)

17. Crinò L, Cappuzzo F, Zatloukal P, et al: Gefitinib versus vinorelbine in chemotherapy-naïve elderly patients with advanced non–small-cell lung cancer (INVITE): A randomized, phase II study. J Clin Oncol 26:4253-4260, 2008

18. Lilenbaum R, Axelrod R, Thomas S, et al: Randomized phase II trial of erlotinib or standard chemotherapy in patients with advanced non–small-cell lung cancer and a performance status of 2. J Clin Oncol 26:863-869, 2008

19. Morère JF, Bréchot JM, Westeel V, et al: Randomized phase II trial of gefitinib or gemcitabine or docetaxel chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2 or 3 (IFCT-0301 study). Lung Cancer 70:301-307, 2010

20. Hidalgo M, Siu LL, Nemunaitis J, et al: Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol 19:3267-3279, 2001

21. Wacker B, Nagrani T, Weinberg J, et al: Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies. Clin Cancer Res 13:3913-3921, 2007

DOI: 10.1200/JCO.2013.52.8794; published online ahead of print at www.jco.org on February 3, 2014

Reply to E.R. Haspinger et al

We respectfully disagree with the premise put forth by Haspinger et al[1] that sufficient advancement has already occurred in epidermal growth factor receptor (*EGFR*) mutation–positive lung cancer. We believe ongoing research will continue to improve outcomes for patients and lead directly and tangentially to further scientific breakthroughs.

Although we appreciate that *EGFR* mutation–positive patients represent a fraction of the overall population with lung cancer, this group should still be studied in depth and afforded the benefit of drug development efforts. In the United States and Europe, *EGFR* mutants comprise 15% to 20% of lung adenocarcinomas, and in Asia its frequency reaches 60% and higher, globally making this genomic alteration frequent enough to efficiently complete nine randomized trials in just a few years.

The discovery of *EGFR* mutations in 2004 not only affected treatment for patients with this mutation, but also permanently and significantly transformed the paradigm of solid tumor biologic research and rapid drug development.This has led to major advances in the treatment of anaplastic lymphoma kinase– and *ROSI*-positive lung cancers and other solid cancers such as malignant melanoma or gastrointestinal stromal tumors.

The solid body of evidence for initial EGFR tyrosine kinase inhibitor (TKI) treatment generated by the lung cancer research community in the past few years may seem like an obvious conclusion today; however, it was far from standard recommendation or practice 4 years ago. While the preliminary results of the Iressa Pan-Asia Study (IPASS) trial had been reported in abstract form at the time of LUX-Lung 3 initiation, neither the detailed publication nor any results from the subsequent trials with gefitinib or erlotinib were yet known. At that time, there was still a fair amount of controversy about the concept of first-line genotype-directed therapy for EGFR, and until our publication there were still no data comparing an EGFR TKI with cisplatin/pemetrexed, currently the preferred chemotherapy regimen for lung adenocarcinoma.

With reference to the tables by Haspinger et al, we would like to caution against any indirect comparisons of efficacy and safety across trials. There are many variables in patient selection and trials methodology that substantially differ among studies and could bias the results; any systematic review of these data should also evaluate the limitations and the potential bias of the comparison. Did the study accept all *EGFR* mutations or only the common mutations known to be most sensitive to EGFR TKIs (del19, L858R)? Was *EGFR* mutation testing done centrally using validated methods or by local academic laboratories? Was imaging performed at similar intervals, and was there a blinded independent review of progression events? Were the analyses done in an intent-to-treat manner or a post hoc retrospective manner?

The initial publication of the primary data from the LUX-Lung 3 study cannot provide all the answers to all the crucial questions about how to best integrate afatinib into existing treatment algorithms for lung cancer. Indeed, data about outcomes for patients with less common mutations and de novo T790M were recently presented at the 2013 World Congress for Lung Cancer meeting, and at the time of this correspondence, other studies are in progress examining afatinib alone and in combination with other therapeutics in various settings, including head-to-head comparisons with gefitinib and erlotinib. Just as the current state of evidence for use of gefitinib, erlotinib, crizotinib, and the approved chemotherapies for lung cancer has not been generated overnight but has continued to amass and become more refined over time, so will data regarding afatinib. We anticipate that going forward other EGFR inhibitors will also emerge, some of which already appear to have marked activity in patients with acquired resistance to earlier EGFR TKIs.

James Chih-Hsin Yang
National Taiwan University Hospital, Taipei, Taiwan

Lecia V. Sequist
Massachusetts General Hospital and Harvard Medical School, Boston, MA

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** James Chih-Hsin Yang, Boehringer Ingelheim (U), Eli Lilly (U), Novartis (C), Roche (C), AstraZeneca (C), Pfizer (C), Takeda Pharmaceuticals (C), Clovis Oncology (C), TTY Biopharm (C),