

# Management of patients with advanced non-small cell lung cancer: role of gefitinib

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**Abstract:** Gefitinib is the first epidermal growth factor receptor tyrosine-kinase inhibitor approved for the treatment of advanced non-small cell lung cancer (NSCLC). Its failure to improve survival in a placebo-control study, however, led to its withdrawal in the United States though it is available in many other countries. Subsequent studies nevertheless showed comparable efficacy for gefitinib and docetaxel in the second-line therapy. Gefitinib significantly improved progression-free survival compared to chemotherapy in patients with activating mutations in the epidermal growth factor receptor tyrosine kinase mutations. This review will discuss the results of these large randomized studies and discuss the role of gefitinib in the treatment of advanced NSCLC.

**Keywords:** gefitinib, non-small cell lung cancer

## Introduction

Lung cancer is the most common cause of cancer mortality in the United States, with 159,390 deaths estimated for the year 2009 by the American Cancer Society, accounting for 30% of cancer deaths in men and 26% of cancer deaths in women.<sup>1</sup> Approximately 87% of patients have one of the non-small cell lung cancer (NSCLC) histology subtypes.<sup>2</sup> The majority of patients present with locally advanced or metastatic disease,<sup>3</sup> and relapses are common in those undergoing resection with curative intent, even with the use of adjuvant chemotherapy.<sup>4</sup> Treatment for patients with advanced disease is largely palliative, and the benefits appear to have reached a plateau with conventional platinum-based chemotherapy doublets.<sup>5</sup> Inhibitors of epidermal growth factor receptor (EGFR) tyrosine kinase (TK) gefitinib and erlotinib are widely used in the treatment of advanced NSCLC. This review will focus on the role of gefitinib in the treatment of patients with advanced NSCLC.

EGFR is a transmembrane glycoprotein, consisting of three main components, including an extracellular ligand-binding domain, a transmembrane region, and a tyrosine kinase (TK) region. Binding of one of the ligands to the extracellular domain, including epidermal growth factor (EGF), transforming growth factor alpha (TGF- $\alpha$ ), beta-cellulin, epiregulin and amphiregulin, leads to receptor dimerization and activation of the TK. The autophosphorylation triggered by the TK promotes multiple intracellular signaling pathways, ultimately causing cancer cell proliferation, invasion, and metastases.<sup>6</sup> The EGFR pathway may be inhibited by a monoclonal antibody that prevents the ligand binding or by a small molecule that inhibits the TK activity.

Gefitinib is a low-molecular-weight, synthetic anilinoquinazoline compound that inhibits autophosphorylation and downstream signaling by reversibly binding to the

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ATP site. Initial pharmacokinetic studies in healthy male volunteers aged 18 to 62 years receiving escalating doses from 1 mg to 75 mg or 100 mg daily for 3 days, or evaluating the effect of food intake after a single dose of 50 mg, showed a peak plasma drug concentration ( $C_{max}$ ) between 3 and 7 hours after administration, with a terminal elimination half-life of 28 hours.<sup>7</sup> The  $C_{max}$  was decreased by 34% with food ingestion, and the prolonged half-life suggested the feasibility of once daily administration. Overall, the treatment was well tolerated, with a similar frequency of adverse effects compared to placebo.

## Phase I clinical trials with gefitinib

The early experience with gefitinib in four open-label multicenter phase I trials included patients with a variety of solid tumors known to have high expression of EGFR, such as NSCLC, breast, head and neck, colon, and ovarian tumors, although individual malignancies were not tested for baseline EGFR.<sup>8–11</sup> Treatment was overall well tolerated, with the most common adverse events including rash, diarrhea, nausea, anorexia, and asthenia. The lowest dose associated with tumor response was 150 mg daily, and the maximum tolerated dose was established at 700 mg daily. Given concerns of sub-therapeutic dose administration in some patients due to pharmacokinetic variability, the lowest dose chosen for phase II clinical trials was 250 mg daily. The alternative dose of 500 mg daily was selected as the highest tolerated dose by most patients. Among the 100 patients with NSCLC enrolled in the combined 4 studies, 24 achieved stable disease and 10 had partial response.

## Single-agent gefitinib in pretreated patients

The efficacy of gefitinib in NSCLC was evaluated in two multicenter phase II trials, the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) studies I and II. Both studies were non-placebo controlled and evaluated gefitinib at doses of 250 mg or 500 mg daily. The IDEAL-I trial, conducted in 43 centers worldwide, had approximately 50% of patients from Japan and enrolled patients who had one or two previous chemotherapy regimens, including a platinum-based combination.<sup>12</sup> There were no significant differences for the dose of 250 mg compared to 500 mg, with similar response rates (18.4% versus 19%), disease control rate (54.4% versus 51.4%), progression-free survival (PFS) (2.7 months versus 2.8 months), median overall survival (7.6 months versus 8 months), and 1-year survival (35% versus 29%). Response rates were significantly better for Japanese patients compared to non-Japanese (27.5% versus

10.4%;  $P = 0.002$ ). The IDEAL-II trial was conducted in 30 US centers and enrolled patients with advanced NSCLC and progressive disease after two or more regimens, including a platinum agent and docetaxel.<sup>13</sup> Similar to IDEAL-I, there were no differences between the 250 mg and 500 mg daily doses according to response rates (12% versus 10%), median survival (7 months versus 6 months), and projected 1-year survival (27% versus 24%). Treatment was well tolerated in both studies, skin rash being the most common side effect. Since the efficacy was similar between the doses and toxicity was more frequent in patients receiving 500 mg, the lower dose became the standard. Clinical predictors for response included Japanese patients, women, adenocarcinoma histology, never smokers, and good performance status (0 or 1). Based on these results, gefitinib received accelerated Food and Drug Administration (FDA) approval on May 5, 2003, as monotherapy for the treatment of locally advanced or metastatic NSCLC after progression following treatment with platinum-based therapy and docetaxel.<sup>14</sup>

Following accelerated approval in the United States, the FDA mandated postmarketing trials for this agent to evaluate its efficacy in prolonging survival in comparison to best supportive care. In the Iressa Survival Evaluation in Lung Cancer (ISEL) trial,<sup>15</sup> a randomized phase III study enrolling patients aged 18 or older, with advanced NSCLC previously treated with 1 or 2 previous regimens and refractory (progressive disease within 90 days from the last treatment dose) or intolerant to the last treatment, were randomized to gefitinib 250 mg daily or placebo in a ratio of 2 to 1. A total of 1692 eligible patients were accrued from 28 countries worldwide. The groups were well balanced, 50% received at least 2 prior chemotherapies, and 90% of the patients were refractory to the last chemotherapy. After a median follow-up of 7.2 months, there was no significant benefit for gefitinib compared to placebo according to median survival (5.6 months versus 5.1 months) or estimated 1-year survival (27% versus 21%) (hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.77–1.02;  $P = 0.087$ ). Similarly, despite numerically superior median survival (6.3 months versus 5.4 months) and 1-year survival (30% versus 18%), the benefit from gefitinib did not reach statistical significance compared to best supportive care in patients with adenocarcinoma (HR 0.84; 95% CI 0.68–1.03;  $P = 0.089$ ). Although the primary analysis by log rank test did not show survival benefit for the gefitinib arm, the preplanned supportive Cox's regression analysis, with covariate adjustments identical to the log rank test, showed a statistically significant improvement for gefitinib compared to placebo in both overall population ( $P = 0.03$ ) and adenocarcinoma ( $P = 0.033$ ).

Additional pre-planned analyses showed better survival for gefitinib compared to placebo in non-smokers (8.9 months versus 6.1 months;  $P=0.012$ ) and Asians (9.5 months versus 5.5 months,  $P=0.01$ ). On December 17, 2004, AstraZeneca issued a letter to US physicians reporting the lack of survival improvement for gefitinib, urging them to consider other treatment options.<sup>16</sup> Gefitinib was essentially replaced by erlotinib after the results of the BR.21 study,<sup>17</sup> a randomized phase III trial showing improved survival for second-line erlotinib compared to placebo. Although only the erlotinib trial showed a statistically significant survival improvement over placebo, there were similar response rates (8% versus 8.9%), stable disease (32% versus 35%), and 1-year survival (27% versus 31%) for gefitinib and erlotinib, respectively.

## Second-line gefitinib compared to chemotherapy

Four recent studies compared gefitinib 250 mg daily with docetaxel (60–75 mg/m<sup>2</sup> every 3 weeks) in patients with advanced NSCLC (Table 1). The Second-line Indication of Gefitinib in NSCLC (SIGN) trial was an international multicenter trial comparing gefitinib to docetaxel in patients with advanced NSCLC progressing through one previous line of chemotherapy.<sup>18</sup> Between October 2003 and June 2004, 68 patients were randomized to gefitinib and 73 to docetaxel. Response rates, median PFS, and median survival for gefitinib and docetaxel were 13.2% and 13.7%, 3 months and 3.4 months, and 7.5 months and 7.1 months, respectively. Gefitinib was associated with fewer adverse events overall (51.5% versus 78.9%) and grade 3 or 4 toxicity (8.8% versus 25.4%). The Iressa as a Second-line Therapy in Advanced NSCLC (ISTANA) was a multicenter Korean study that enrolled 82 patients to gefitinib and 79 patients to docetaxel.<sup>19</sup> Response rates for gefitinib were signifi-

cantly higher compared to docetaxel (28.1% versus 7.6%;  $P < 0.001$ ). Gefitinib was also associated with increased PFS ( $P=0.044$ ), and the overall survival results are still pending. The V-15-32 study was a multicenter Japanese study enrolling patients with advanced NSCLC previously treated with one or two lines of chemotherapy.<sup>20</sup> Between September 2003 and January 2006, 245 patients were enrolled into the gefitinib arm and 244 to docetaxel. Response rates were significantly superior for the gefitinib arm (22.5% versus 12.8% (OR 2.14; 95% CI 1.21–3.78,  $P=0.009$ ), median PFS was identical in both arms (2 months), and median survival and 1-year survival for gefitinib and docetaxel were 11.5 months and 47.8% and 14 months and 53.7%, respectively. Although there were no statistically significant differences in overall survival ( $P=0.33$ ), the predefined criterion for non-inferiority (upper CI limit for HR  $\leq 1.25$ ) was not achieved (HR 1.12; 95.24% CI 0.89–1.40). Nevertheless, despite the lack of proven non-inferiority, the similar survival and decreased toxicity for gefitinib showed that this agent remained an effective therapy. The Iressa NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST) was a multicenter randomized phase III trial enrolling patients with advanced NSCLC who had been previously treated with a platinum-based chemotherapy.<sup>21</sup> In this large study, 733 patients received gefitinib and 733 received docetaxel. Compared to docetaxel, gefitinib was associated with similar response rates (9.1% versus 7.6%; OR 1.22,  $P=0.33$ ), PFS (2.2 months versus 2.7 months; HR 1.04,  $P=0.47$ ), and median overall survival (7.6 months versus 8 months; HR 1.020; 95% CI 0.905–1.150). This study, unlike the V-15-32, met the predefined non-inferiority criterion, which was determined as the upper confidence limit  $< 1.154$ . Subset analyses showed longer survival for never smokers, women, Asian patients, and those with adenocarcinoma, but this survival

**Table 1** Recent studies comparing gefitinib 250 mg daily with docetaxel (60–75 mg/m<sup>2</sup> every 3 weeks) in patients with advanced NSCLC

Trial (year)	Treatment	Patients	Response (%)	Median PFS (months)	Median OS (months)
SIGN (2005) <sup>18</sup>	Gefitinib	68	13.2	3	7.5
	Docetaxel <sup>a</sup>	73	13.7	3.4	7.1
ISTANA (2008) <sup>19</sup>	Gefitinib	82	28.1%	NR	NR
	Docetaxel <sup>a</sup>	79	7.6%	NR	NR
V-15-32 (2008) <sup>20</sup>	Gefitinib	245	22.5	2	11.5
	Docetaxel <sup>b</sup>	244	12.8	2	14
INTEREST (2008) <sup>21</sup>	Gefitinib	733	9.1	2.2	7.6
	Docetaxel <sup>a</sup>	733	7.6	2.7	8

<sup>a</sup>Docetaxel 75 mg/m<sup>2</sup>

<sup>b</sup>Docetaxel 60 mg/m<sup>2</sup>

**Abbreviations:** PFS, progression-free survival; OS, overall survival; NR, not reported.

prolongation compared to their counterparts was observed in both the gefitinib and docetaxel arms compared to the rest of the population. Similar to the other reported trials, toxicity was significantly lower in the gefitinib arm.

Shepherd and colleagues recently reported the meta-analysis of the four clinical trials comparing gefitinib with docetaxel.<sup>22</sup> In univariate analysis, gefitinib was associated with increased response rates (OR 1.65; 95% CI 1.24–2.21,  $P = 0.0007$ ) but similar PFS (HR 0.96; 95% CI 0.87–1.05,  $P = 0.37$ ) and overall survival (HR 1.03; 95% CI 0.93–1.13,  $P = 0.57$ ). When adjusted for study, smoking history, number of previous chemotherapy regimens, response to prior therapy, gender, age, and performance status, response rates remained significantly better for gefitinib (OR 1.58; 95% CI 1.19–2.10,  $P = 0.001$ ), whereas PFS and overall survival were similar. Taken together, the current data suggest that in the second line setting, gefitinib had similar efficacy as docetaxel but was better tolerated even in molecularly unselected patients with advanced NSCLC.

## Experience with first-line gefitinib in unselected patients

Multiple trials have evaluated the use of gefitinib in previously untreated advanced unselected NSCLC patients (Table 2). Reck and colleagues<sup>23</sup> showed a 5% response rate with 40% stable disease in 58 patients. Median PFS and survival were 7 weeks and 29 weeks, respectively. In contrast, Niho and colleagues<sup>24</sup> showed response rate of 30% in 40 eligible patients, with median survival of 13.9 months and 1-year survival of 55%. Nevertheless, despite encouraging response rates and survival, 4 patients (10%) developed interstitial lung disease, which was considered unacceptable, particularly in the first-line setting. The Iressa in NSCLC versus Vinorelbine Investigation in The Elderly (INVITE) was a multicenter randomized

phase II trial comparing gefitinib to vinorelbine 30 mg/m<sup>2</sup> on days 1 and 8 every 21 days in patients aged 70 or older with chemotherapy-naïve advanced NSCLC.<sup>25</sup> The median PFS, the primary objective of the study, was 2.7 months in patients treated with gefitinib and 2.9 months in those treated with vinorelbine (HR 1.19, 95% CI 0.85–1.65,  $P = 0.31$ ). Median overall survival for gefitinib and vinorelbine were 5.9 months and 8 months, respectively (HR 0.98; 95% CI 0.66–1.47). Treatment was better tolerated in the gefitinib arm. Two large phase III trials evaluated the role of gefitinib in combination to chemotherapy compared to chemotherapy alone in previously untreated patients with advanced NSCLC. In both the Iressa NSCLC Trial Accessing the Combination Treatment (INTACT)-1 trial,<sup>26</sup> in which the control arm included cisplatin and gemcitabine, and the INTACT-2 trial,<sup>27</sup> with carboplatin and paclitaxel, the addition of gefitinib failed to improve response rates, PFS, median survival time, or 1-year survival. In a subset analysis of patients in the INTACT-2 study with adenocarcinoma and receiving treatment for 90 or more days, the median survival for patients in the low-dose gefitinib arm (250 mg day) was significantly higher than placebo (17.1 months versus 13.6 months,  $P = 0.05$ ). These findings suggest that sequential therapy with chemotherapy followed by gefitinib, rather than concurrent, may be the optimal schedule, and there could be a role for maintenance gefitinib.

In the phase III West Japan Thoracic Oncology Group 0203, chemotherapy naive patients with advanced NSCLC were randomized to receive either platinum doublet for up to 6 cycles or 3 cycles of the same chemotherapy followed by gefitinib daily until disease progression.<sup>28</sup> Although there was an improvement in the PFS for patients treated with maintenance gefitinib (4.6 versus 4.2 months,  $P < 0.001$ ), overall survival, the primary endpoint did not reach statistical significance (13.6 versus 12.8 months,  $P = 0.10$ ). In the

**Table 2** First-line gefitinib in advanced NSCLC

Trial/author (year)	Phase	Treatment	Patients	Response (%)	Median PFS/TTP (months)	Median OS (months)
Reck (2006) <sup>23</sup>	II	Gefitinib	58	5	1.7	6.7
Niho (2006) <sup>24</sup>	II	Gefitinib	40	30	NA	13.9
INVITE (2008) <sup>25</sup>	III	Gefitinib	97	3.1	2.7	5.9
		Vinorelbine	99	5.1	2.9	8
INTACT-1 (2004) <sup>26</sup>	III	CpGm	324	47.2	6	10.9
		CpGmGefitinib 250	336	51.2	5.8	9.9
		CpGmGefitinib 500	330	50.3	5.5	9.9
INTACT-2 (2004) <sup>27</sup>	III	CbPc	345	30	5	9.9
		CbPcGefitinib 250	345	30.4	5.3	9.8
		CbPcGefitinib 500	347	28.7	4.6	8.7

**Abbreviations:** Cb, carboplatin; Cp, cisplatin; Gm, gemcitabine; Pc, paclitaxel; PFS, progression-free survival; TTP, time to progression; NR, not reported.

subset of patients with adenocarcinoma however, the gefitinib use was associated with better overall survival (15.4 versus 14.3 months,  $P = 0.03$ ).

## Patient selection for gefitinib

Since initial trials showed improved responses in never smokers, patients with *EGFR* mutation, and bronchioloalveolar histology (BAC), subsequent studies were developed for these specific patient populations (Table 3).

In the multicenter phase II ONCOBELL study<sup>29</sup> enrolling patients who were never smokers or had *EGFR* positive by fluorescence in situ hybridization (FISH) and p-AKT positive irrespective of smoking status, the response rate and 1-year survival in the 42 available patients were 48% and 64% respectively.

In the randomized phase III Iressa Pan-Asia Study (IPASS), previously untreated patients with adenocarcinoma and history of smoking either less than 100 cigarettes in their lifetime (non-smokers) or 10 pack-year or less quitting tobacco for at least 15 years (former light smokers) were randomized to receive first-line gefitinib 250 mg daily or carboplatin plus paclitaxel.<sup>30</sup> Response rates were higher for the gefitinib arm in both the overall population (43% versus 33%,  $P < 0.001$ ) and in patients with *EGFR* mutation (71.2% versus 47.3%,  $P < 0.001$ ). In contrast, the response rate was significantly lower for gefitinib compared to chemotherapy in patients without the *EGFR* mutation (1.1% versus 23.5%,  $P = 0.001$ ). PFS in patients receiving gefitinib was significantly improved in those with *EGFR* mutation (HR for progression 0.48; 95% CI, 0.36–0.64;  $P < 0.001$ ) but significantly worse in those without the mutation (HR

1.85; 95% CI 2.05–3.98;  $P < 0.001$ ). Significant response rates and survival were also observed in a Korean study, where 55% of the 72 patients achieved survival and 76% were alive at 1 year.<sup>31</sup>

The two studies evaluating the role of single agent gefitinib in patients with BAC showed response rates of 13% to 17%, median survival of 13 to 13.3 months, and 1-year survival rates of 51 to 55%.<sup>32,33</sup>

In addition to clinical correlates, such as ethnicity, gender, histology, and smoking status, several molecular features that are associated with response to *EGFR* TKIs have been reported. The first predictor for response discovered was the activating *EGFR* mutations in a small region of the *EGFR* gene encoding the tyrosine kinase domain.<sup>34,35</sup> The most common of these mutations are an in-frame deletion of exon 19 and a missense mutation at codon 858 resulting in arginine–leucine substitution (L858R). Several studies showed significant improvement in response rates among patients with activating *EGFR* gene mutation treated with gefitinib. Small trials, mostly from Japan and enrolling between 16 and 28 patients with *EGFR* mutation, showed response rates ranging from 50% to 90%, and PFS from 7.7 months to 13 months.<sup>36–40</sup> In the two studies reporting 1-year survival, it ranged between 79% and 88%. In the larger, predominantly non-Asian, iTARGET study,<sup>41</sup> the response rate and 1-year survival for patients NSCLC harboring the *EGFR* mutation and treated with first-line gefitinib were 55% and 73% respectively.

*EGFR* gene amplification has also been associated with response to gefitinib. The *EGFR* gene is located in the chromosome 7 and may be detected by FISH. Cappuzzo and colleagues<sup>42</sup> showed that true gene amplification by FISH in

**Table 3** Single-agent gefitinib in selected patients

Study/author (year)	Setting	Patients	Response (%)	PFS/TTP (months)	Median survival (months)	1-year survival
ONCOBELL (2007) <sup>29</sup>	Never-smokers <sup>a</sup>	42	48	6.4	NR	64
Lee (2006) <sup>31</sup>	Never-smokers	55	61	6.5	NR	79
iTARGET (2008) <sup>41</sup>	<i>EGFR</i> mutation	31	55	9.2	17.5	73
Asahina (2006) <sup>36</sup>	<i>EGFR</i> mutation	16	75	8.9	NR	88
ONCOBELL (2007) <sup>29</sup>	<i>EGFR</i> mutation	42	48	6.4	NR	64
Inoue (2006) <sup>37</sup>	<i>EGFR</i> mutation	16	75	9.7	NR	NR
Sutani (2006) <sup>38</sup>	<i>EGFR</i> mutation	27	78	9.4	15.4	NR
Sunaga (2007) <sup>39</sup>	<i>EGFR</i> mutation	19	84	13	NR	NR
Tamura (2008) <sup>40</sup>	<i>EGFR</i> mutation	28	75	11.5	NR	79
West (2006) <sup>32</sup>	BAC	101	17	4	13	51
Cadranel (2007) <sup>33</sup>	BAC	88	13	2.9	13.3	55

<sup>a</sup>Patients were also enrolled if they had *EGFR* and p-AKT mutations regardless of smoking status.

**Abbreviations:** *EGFR*, epidermal growth factor receptor; PFS, progression-free survival; TTP, time to progression; NR, not reported; BAC, bronchioloalveolar carcinoma.



patients treated with gefitinib (tight *EGFR* genes clusters and a ratio of *EGFR* gene to chromosome  $\geq 2$ , or  $\geq 15$  copies of *EGFR* per cell in 10 or more of the analyzed cells), or high polysomy ( $\geq 4$  copies in  $\geq 40\%$  of cells) were associated with improved response rates (36% versus 3%,  $P < 0.001$ ), time to progression (9 versus 2.2 months,  $P < 0.001$ ) and median survival (18.7 versus 10.3 months,  $P = 0.03$ ) compared to those without these features. In Oncobell study,<sup>29</sup> patients with *EGFR* FISH positive status had response rates of 68% (vs 9.1% in *EGFR* FISH negative) and TTP of 7.6 months (vs 2.7 months in *EGFR* FISH negative). In the retrospective analysis of the ISEL study,<sup>15</sup> survival patients treated with gefitinib was improved compared to placebo in patients with *EGFR* amplification by FISH (8.3 versus 4.5 months,  $P = 0.067$ ) and decreased in those low *EGFR* gene copy (4.3 versus 6.2 months,  $P = 0.417$ ).<sup>43</sup> These results contrast to the In the INTEREST trial,<sup>21</sup> where there was no benefit from the use of gefitinib, compared to docetaxel in patients with *EGFR* mutation.

Polymorphisms related to the *EGFR* pathway have been studied to predict response to *EGFR* TKIs. The intron 1 CA repeat polymorphism has been most studied. Shorter CA repeats are associated with higher response rates and survival in patients treated with *EGFR* TKIs.<sup>44,45</sup>

*K-ras* mutations, which are mutually exclusive with *EGFR* mutations in lung cancer, are most commonly seen in smokers and associated with resistance to gefitinib. Among multiple studies evaluating the use of gefitinib or erlotinib in patients with *K-ras* mutations, mutations were found in approximately 17% of patients by pooled analysis, with most trials showed no response to TKIs.<sup>46</sup> Although *K-ras* mutations have been strongly associated with cigarette smoking, a recent study on 482 lung adenocarcinomas showed the presence of *K-ras* mutations 15% of never smokers, 22% of former smokers, and 25% of current smokers.<sup>47</sup>

## Summary

Despite the withdrawal of gefitinib in the United States after the results from the ISEL study,<sup>15</sup> gefitinib continues to be evaluated in multiple studies and has been shown to have comparable efficacy to standard chemotherapy in the second-line setting. Gefitinib produces stellar and striking results in patients with lung cancer whose tumor cells harbor activating mutations in *EGFR* TK domain and has now been approved for use in Europe in this molecularly selected population.

## Disclosures

Dr Ramaswamy Govindan has served as a consultant for AstraZeneca and Genentech.

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