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Real-world usage and clinical outcomes of alectinib among post-crizotinib progression anaplastic lymphoma kinase positive non-small-cell lung cancer patients in the USA

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Background: Alectinib is an approved treatment for anaplastic lymphoma kinase (ALK)-positive patients with advanced non-small-cell lung cancer. Despite positive supporting clinical data, there is a lack of real-world information on the usage and patient outcomes of those treated with alectinib post-crizotinib progression.

Methods: Participating oncologists (N=95) in the USA were recruited from an online physician panel to participate in a retrospective patient chart review. Physicians randomly selected eligible patients (ie, patients who progressed on crizotinib as their first ALK inhibitor and were treated with alectinib as their second ALK inhibitor), collected demographics and clinical history from their medical charts, and entered the data into an online data collection form.

Results: A total of N=207 patient charts were included (age: 60.1±10.4 years; 53.6% male). The patients in our sample were older (median age of 60 vs 53 years), were more likely to be current smokers (12% vs 1%), had better performance status (45% vs 33% had an Eastern Cooperative Oncology Group [ECOG] of 0), and were less likely to have an adenocarcinoma histology (83% vs 96%) relative to published clinical trials. The objective response rate was higher than in clinical trials (67.1% vs 51.3%, respectively) as was the disease control rate (89.9% vs 78.8%, respectively), though it varied by race/ethnicity, ECOG, and prior treatment history. Discontinuation (0.0%) and dose reductions (3.4%) due to adverse events were uncommon in alectinib.

Conclusion: Patients using alectinib post-crizotinib in clinical practice are older, more racially/ethnically and histologically diverse than patients in published trials. Real-world response rates were high and similar to those reported in clinical studies, though there is some variation by patient characteristics. Alectinib was well tolerated in clinical practice as reflected by the rates of discontinuation, dose reductions, and dose interruptions.

Keywords: alectinib, anaplastic lymphoma kinase, non-small-cell lung cancer, treatment patterns, outcomes, ALK inhibitor, ALK+

Introduction

An estimated 220,000 adults were diagnosed with lung and bronchus cancer in the USA in 2015, representing 13% of all new cancer cases.¹ Non-small-cell lung cancer (NSCLC) accounts for ~80%–85% of all cases of lung cancer, and is the most common cause of death in men and second only to breast cancer in women.² Prognosis is poor for patients with metastatic disease, with the median survival <1 year because of delays in diagnosis.^{3,4}

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Treatment of NSCLC is guided by disease stage, histology, and mutation status. Surgery is the most common treatment for early-stage localized disease, whereas multimodal therapy remains the norm for patients with locally advanced disease.⁵ Approximately 40% of patients with NSCLC present with metastatic or locally advanced disease, underscoring the importance of identifying therapeutic regimens that may benefit this large patient population. Combination chemotherapy, usually platinum-based, has historically been the first-line therapy of choice for advanced NSCLC among patients without driver mutations.^{6–8} Newer agents, such as programmed cell death-1 and programmed cell death ligand-1 inhibitors, have been more recently evaluated in clinical trials for the treatment of NSCLC and several other types of cancer.^{9–11}

Over the last decade, a variety of targeted therapies have been developed for the treatment of advanced or metastatic NSCLC in patients with driver mutations. Indeed, anaplastic lymphoma kinase (ALK) inhibitors represent a promising potential target for antitumor therapy,^{12–14} with ~2%–7% of patients with NSCLC being ALK positive.^{7,15} Crizotinib was identified as the first potent inhibitor of ALK in experimental cancer models;¹⁶ clinical data have suggested superior response and longer progression-free survival for patients treated with crizotinib relative to chemotherapy.^{17–20}

Despite these efficacy results, almost all patients ultimately develop resistance to crizotinib within 1–2 years, with the central nervous system (CNS) being a frequent site of progression.^{21–24} The recently available second-generation ALK inhibitors (eg, ceritinib, alectinib, brigatinib) and third-generation ALK inhibitors (eg, lorlatinib) have been found to provide significant benefits for patients who experience crizotinib progression.^{25,26} Of the second-generation ALK inhibitors, alectinib is the only one that is not exported out of the CNS because of it not being a p-glycoprotein substrate,^{25–27} and several clinical studies^{28–31} have shown alectinib to be highly active, especially in patients with brain metastases and CNS disease. Further, alectinib is well tolerated among crizotinib-resistant patients.^{28–31} However, little real-world data exist on the usage and outcomes of patients treated with alectinib after crizotinib progression. The aim of the present study is to examine the real-world treatment patterns and clinical outcomes of patients with ALK+ NSCLC who have progressed on crizotinib and were treated with alectinib as their second ALK inhibitor.

Methods

Data source

A retrospective patient chart review study was conducted to meet the objectives described above. Participating oncologists

were recruited from the Medefield physician panel (<http://www.medefield.com/>). The Medefield panel is an opt-in panel in which physicians join with the understanding that they will complete periodic surveys. All panel physicians in the USA have their credentials validated with American Medical Association.

Potential physician respondents were emailed an invitation to participate in the study. Physicians who provided informed consent were screened for eligibility. Physicians' inclusion criteria include board-certified or board-eligible oncologist, in practice for at least 5 years but no more than 25 years, personally involved in the treatment decisions of patients with NSCLC, and have seen at least 1 NSCLC ALK+ patient in the past year. Physicians who met inclusion criteria were then asked to select between 1 and 5 of their patient charts that met the following eligibility criteria: ≥ 18 years, diagnosed with ALK+ NSCLC (tumors harboring a rearranged ALK gene/fusion protein), and experienced disease progression while on crizotinib (as their first ALK inhibitor). ALK+ status was determined by the responding physician based on results available in the patient chart. It was desired to have a minimum of 12-month follow-up from time of initial disease progression on crizotinib or until death (if < 12 months of follow-up exist). Patients who participated in an NSCLC-related clinical trial prior to crizotinib and alectinib were excluded.

Using the data available from each medical chart, the physician collected the demographics, health history, health care resource use, and treatment information for each patient. Data were pulled from notes from physical examinations, laboratory data, imaging data, prescription data, and nurse records, as appropriate.

Ethics

The study protocol and data collection form were reviewed by an independent institutional review board (Pearl IRB, Indianapolis, IN; Protocol #: 16-033202) and the study was granted exemption status. The IRB reviewed the documents submitted for exemption determination in accordance to the US Food and Drug Administration 21 CFR 56.104 and the Department of Health and Human Services 45 CFR 46.101 regulations. The exemption was approved under the exempt review category 45 CFR 46.101(b) category 4.

Patient written informed consent to review the medical records was not required by the IRB as no personally identifiable patient information was collected. Only anonymous patient data were collected and results were only reported in aggregate. Physicians provided consent for participating in the study and written informed consent was required from each responding physician, before participating in the study.

Study sample

Data from a total of N=207 patient charts who used alectinib as their second ALK inhibitor were collected from N=95 physicians.

Study measures

Physician demographics: Physicians provided information as to their age, sex, and practice characteristics (years in practice, setting, and patient load).

Patient demographics: Physicians provided information related to the age, sex, and employment status of each patient.

General health history: Height and weight (to convert to body mass index [BMI] category), smoking history, and comorbidities (to calculate a Charlson comorbidity index) were assessed.

NSCLC history: The date of diagnosis, stage at diagnosis, histology, current performance status (Eastern Cooperative Oncology Group [ECOG]), and the number/location/date of metastases were captured.

Treatment history: Treatments used prior to and after crizotinib, including their duration, were captured. Reasons for discontinuation of each therapy were captured along with the presence and reasons for dose modifications. The presence of adverse events was captured along with treatments related to brain/CNS metastases.

Clinical outcomes: Best response (complete response [CR], partial response [PR], stable disease [SD], or progression) was captured for each treatment based on the interpretation of the treating physician using the data contained within the medical chart. The study did not mandate that any specific criteria, such as RECIST v1.1, were to be used in this assessment. For the purposes of this study, objective response rate (ORR) was defined as the proportion of patients achieving a best response of CR or PR. Disease control rate (DCR) was defined as the proportion of patients achieving a best response of CR, PR, or SD.

Health care resource use: The number of hospitalizations, emergency room visits, and office visits was captured. Health care resource use specific to adverse events was also assessed.

Statistical analysis

Physician and patient characteristics, response rates, and safety/tolerability were reported descriptively using frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Differences in response rates across patient characteristic strata were compared using chi-square tests.

Results

Physician characteristics

A total of N=95 physicians contributed patient charts; N=47 (49.5%) specialized in hematology/oncology and N=48 (50.5%) specialized in medical oncology (Table 1). Physicians were predominantly male (81.1%), with a mean of 14.6 years (SD=6.4) in practice. The most common practice setting was private practice (46.3%) followed by an academic hospital/medical center (35.8%).

Real-world vs clinical trial patient characteristics

Descriptive comparisons were then made between our study and available clinical trial results (Table 2).^{28,29} Key differences observed between our study and clinical trial populations included age (median age of 60 vs 53 for our study and the pooled clinical trial samples, respectively), gender (54% vs 44% male, respectively), and performance status (45% vs 33% had an ECOG of 0). Both our study and clinical trial samples had similar percentages of Asian patients (18% vs 19%). Patients in our study were more likely to be a current smoker (12% vs 1%), less likely to have an adenocarcinoma histology (83% vs 96%), and were less likely to have presented with brain metastases (12% vs 60%) relative to clinical trial samples.

Comparisons were also made between alectinib best overall responses rates in our study and clinical trial data (Table 3). Among the full sample (N=207 alectinib patients),

Table 1 Characteristics of the physician sample treating patients with alectinib post-crizotinib progression (N=95)

Characteristics	Total sample (N=95)
Physician gender	
Male (%)	77 (81.1)
Female (%)	18 (18.9)
Physician age	
<40 years (%)	19 (20.0)
41–50 years (%)	49 (51.6)
51–60 years (%)	22 (23.2)
61–70 years (%)	5 (5.3)
Physician specialty	
Medical oncology (%)	47 (49.5)
Hematology/oncology (%)	48 (50.5)
Years of practice in specialty	
Mean ± Standard deviation	14.6±6.4
Median (min–max)	15 (5.0–30.0)
Primary clinical practice	
Private practice (%)	44 (46.3)
Academic hospital/medical center (%)	34 (35.8)
Nonacademic hospital/medical center (%)	10 (10.5)
Comprehensive cancer center (%)	7 (7.4)

Table 2 Differences in patient characteristics between clinical trial samples and the current study sample among those using alectinib post-crizotinib progression

Characteristics	Alectinib group in Ou et al ²⁸	Alectinib group in Shaw et al ²⁹	Pooled analysis in Yang et al ³⁰	Alectinib group in study sample
N	138	87	225	207
Patient age (years)				
Mean \pm Standard deviation	51.5 \pm 11.1	N/A	N/A	60.1 \pm 10.4
Median (min–max)	52.0 (22.0–79.0)	54.0 (29.0–79.0)	53.0 (22.0–79.0)	60 (25–86)
Sex				
Male (%)	61 (44)	39 (45)	100 (44)	111 (53.6)
Female (%)	77 (56)	48 (55)	125 (56)	96 (46.4)
Race/ethnicity				
Non-Hispanic White/Caucasian (%)	93 (67)	73 (84)	166 (74)	113 (54.6)
Asian (%)	36 (26)	7 (8)	43 (19)	37 (17.9)
Non-Hispanic Black/African American (%)			4 (2)	29 (14.0)
Hispanic (%)				25 (12.1)
Other (%)	9 (7)	7 (8)	12 (5)	3 (1.5)
Smoking status				
Current smoker (%)	3 (2)	0 (0)	3 (1)	24 (11.6)
Former smoker (%)	39 (28)	33 (38)	72 (32)	86 (41.6)
Never smoker (%)	96 (70)	54 (62)	150 (67)	81 (39.1)
Passive (second-hand) smoker (%)	0 (0)	0 (0)	0 (0)	13 (6.3)
Unknown (%)	0 (0)	0 (0)	0 (0)	3 (1.5)
NSCLC histological subtype				
Adenocarcinoma (%)	133 (96)	82 (94)	215 (96)	172 (83.1)
Epidermoid or squamous cell carcinoma (%)	2 (1)	5 (6)	10 (4)	11 (5.3)
Large cell carcinoma (%)	3 (2)			16 (7.7)
ECOG at crizotinib initiation				
0 (%)	44 (32)	30 (35)	74 (33)	94 (45.4)
1 (%)	81 (59)	48 (55)	129 (57)	84 (40.6)
2 (%)	13 (9)	9 (10)	22 (10)	18 (8.7)
3 (%)	0 (0)	0 (0)	0 (0)	10 (4.8)
Treatments prior to crizotinib				
Chemotherapy (%)	110 (80)	64 (74)	174 (77)	45 (22)
Baseline CNS metastases	83 (61)	52 (60)	136 (60)	25 (12.1)
Follow-up period, months (min–max)	3.9–14.1 (primary) 8.7–18.9 (updated)	1.1–13.6 (primary) 1.1–19.9 (updated)	N/A	0.0–10.0

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; N/A, not applicable; NSCLC, non-small-cell lung cancer.

the ORR was higher than in clinical trials (67.1% vs 51.3%, respectively) as was the DCR (89.9% vs 78.8%, respectively).

Best overall response rates in the overall alectinib sub-sample were then compared across various patient characteristic strata (Table 4). As reported above, best overall response rates were consistent, and in some cases higher than those reported in prior clinical trials.^{28,29} Although response did not differ by physician characteristics or patient age, ORR was highest among Asian respondents (89.2%) vs 47.4% among non-Asian/non-White respondents ($P<.05$). These findings are consistent with those reported in clinical trials.^{28,29} Former/passive/never smokers exhibited higher response rates relative to current smokers (ORR =68.3% vs 58.3%) but this difference was not significant ($P=0.07$). No differences were observed by level of BMI ($P=0.81$).

Better functional status, as assessed by ECOG performance score, was associated with better response (ORR =71.6% for ECOG 0–1 vs 30.0% for ECOG 2+; $P<0.05$). Finally, ORR was similar between those with and without prior chemotherapy (65.9% vs 67.5%, respectively); however, rates of SD were higher (25.8% vs 11.4%) and rates of PD were lower (6.7% vs 22.7%) for those without prior chemotherapy ($P<0.05$).

Dose modifications

The median dose for the patients in this study was 600 mg twice daily. Discontinuations were the most common category of dosage modification. Among those who used alectinib, 14.0% of patients ($N=29$) discontinued the drug, whereas only 4.3% ($N=9$) had their dose reduced; and only one patient experienced a dose interruption ($N=1$; 0.5%

Table 3 Differences in best overall systemic response rate between clinical trial samples and the current study sample among those using alectinib post-crizotinib progression

Types of response rate	Alectinib group in Ou et al ²⁸ (response-evaluable population)	Alectinib group in Shaw et al ²⁹ (primary analysis)	Pooled analysis in Yang et al ³⁰	Alectinib group in study sample
N	122	67	189	207
Complete response (%)	0 (0.0)	0 (0.0)	0 (0.0)	14 (6.8)
Partial response (%)	61 (50.0)	35 (52.2)	97 (51.3)	125 (60.4)
Stable disease (%)	35 (28.7)	18 (26.9)	52 (27.5)	47 (22.7)
Progressed disease (%)	22 (18.0)	11 (16.4)	N/A	21 (10.1)
Unknown/indeterminate (%)	4 (3.3)	3 (4.5)	N/A	0 (0.0)
Objective response rate (%)	61 (50.0)	35 (52.2)	97 (51.3)	139 (67.1)
Disease control rate (%)	96 (78.7)	53 (79.1)	149 (78.8)	186 (89.9)

Abbreviation: N/A, not applicable.

[Table 5]). Of the dose discontinuations, N=12 (41.4%) were due to disease progression, 9 (31.0%) were due to death, N=5 (17.2%) were due to patient request, and N=3 (10.3%) were due to other reasons (none were due to adverse events).

Safety and tolerability

There were no dose discontinuations or dose reductions due to adverse events among the patients in this study. Of the dose reductions, N=7 (3.38%) were due to adverse events;

Table 4 Differences in best overall systemic response rate across patient characteristic strata among those using alectinib post-crizotinib progression (N=207)

Characteristics	N	Complete response (%)	Partial response (%)	Stable disease (%)	Progressive disease (%)	P-value
Treatment setting						0.173
Nonacademic	102	9.0 (8.8)	57.0 (55.9)	28.0 (27.5)	8.0 (7.8)	
Academic	105	5.0 (4.8)	68.0 (64.8)	19.0 (18.1)	13.0 (12.4)	
Physician specialty						0.435
Hematology/oncology	109	7.0 (6.4)	66.0 (60.6)	28.0 (25.7)	8.0 (7.3)	
Medical oncology	98	7.0 (7.1)	59.0 (60.2)	19.0 (19.4)	13.0 (13.3)	
Age						0.576
<65 years	133	11.0 (8.3)	77.0 (57.9)	32.0 (24.1)	13.0 (9.8)	
≥65 years	74	3.0 (4.1)	48.0 (64.9)	15.0 (20.3)	8.0 (10.8)	
Race/ethnicity						0.001
White	113	11.0 (9.7)	68.0 (60.2)	25.0 (22.1)	9.0 (8.0)	
Asian	37	2.0 (5.4)	31.0 (83.8)	2.0 (5.4)	2.0 (5.4)	
Other	57	1.0 (1.8)	26.0 (45.6)	20.0 (35.1)	10.0 (17.5)	
Smoking status						0.074
Current smoker	24	2.0 (8.3)	12.0 (50.0)	4.0 (16.7)	6.0 (25.0)	
Former/never/passive smoker	183	12.0 (6.6)	113.0 (61.7)	43.0 (23.5)	15.0 (8.2)	
BMI						0.811
Underweight	6	0.0 (0)	3.0 (50.0)	2.0 (33.3)	1.0 (16.7)	
Normal	102	8.0 (7.8)	65.0 (63.7)	18.0 (17.6)	11.0 (10.8)	
Overweight	80	5.0 (6.3)	48.0 (60.0)	20.0 (25.0)	7.0 (8.8)	
Obese	19	1.0 (5.3)	9.0 (47.4)	7.0 (36.8)	2.0 (10.5)	
CCI						0.569
0	96	8.0 (8.3)	61.0 (63.5)	18.0 (18.8)	9.0 (9.4)	
1	62	5.0 (8.1)	37.0 (59.7)	14.0 (22.6)	6.0 (9.7)	
2+	49	1.0 (2.0)	27.0 (55.1)	15.0 (30.6)	6.0 (12.2)	
ECOG						0.009
0–1	102	7.0 (6.9)	66.0 (64.7)	25.0 (24.5)	4.0 (3.9)	
2+	10	0.0 (0)	3.0 (30.0)	3.0 (30.0)	4.0 (40.0)	
Unknown	95	7.0 (7.4)	56.0 (58.9)	19.0 (20.0)	13.0 (13.7)	
Prior chemotherapy						0.006
No prior chemotherapy	163	12.0 (7.4)	98.0 (60.1)	42.0 (25.8)	11.0 (6.7)	
Prior chemotherapy	44	2.0 (4.5)	27.0 (61.4)	5.0 (11.4)	10.0 (22.7)	

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group.

Table 5 Frequency and reasons for dosage modification among patients using alectinib post-crizotinib progression (N=207)

Modification category	Reason	N (%)
Discontinuation (N=29; 14.0%)	Disease progression	12 (41.4)
	Death	9 (31.0)
	Patient request	5 (17.2)
	Other	3 (10.3)
Dose reduction (N=9; 4.3%)	Toxicity	7 (77.8)
	Disease progression	1 (11.1)
	Patient request	1 (11.1)
Dose interruption (N=1; 0.5%)	Patient request	1 (100.0)

specific adverse events included fatigue (N=4), hepatotoxicity (N=2), bradycardia (N=1), and edema (N=1).

Discussion

The objectives of this study were to examine the real-world usage and clinical outcomes among patients with ALK+ NSCLC who were treated with alectinib after progressing on crizotinib as their first ALK inhibitor. The sample characteristics of our study patients vs those of clinical trials patients emphasize the differences between these two environments. The alectinib sample in our study was ~10 years older, had fewer Asian respondents, more African-American and Hispanic respondents, had a more diverse histology (clinical trials were almost exclusively adenocarcinoma), had more current smokers, and had poorer functional status based on ECOG measures than clinical trial samples.^{28,29} Additionally, many alectinib patients were managed by a hematologist/oncologist and in the private practice setting. Although not alectinib specific, recent real-world data studies of ALK+ NSCLC patients suggested similar demographic (age, sex) and health history (smoking status) findings as reported here.^{32,33} These results suggest that the patients prescribed alectinib immediately after crizotinib progression are more demographically diverse than those enrolled in clinical trials, which could have implications for clinical outcomes and experiences with safety/tolerability events.

Rates of brain metastases in our study vis-à-vis published literature deserve specific comment. Some real-world studies have reported brain metastatic rates over 50%,³⁴ which is similar to that reported in clinical studies.^{28–30} However, other real-world studies have estimated rates closer to 20%–30%.^{33,35–37} These numbers are still higher than those reported in our sample in which 12% of patients had brain metastases at the end of crizotinib/initiation of alectinib. Although it is unknown what could cause the discrepancy, there are

several possibilities. First, the follow-up time (as well as the timeframe that constituted “baseline”) was slightly shorter in the present study (eg, relative to Betts et al³³); thus, there was less time for a brain metastasis to manifest. Secondly, our patient population was generally older than the available clinical data, and research has suggested that the incidence of brain metastases in older patients is lower than that in younger patients.³⁸ Recent studies have suggested that only 47% of brain metastases are symptomatic³⁹ representing a possible source of underdiagnosis of brain metastases that is disproportionately more common in smaller practices than larger academic centers. Most of the patients in this study were treated in smaller private practices, which could have contributed to the lower rates of brain metastasis. Undoubtedly, more research is necessary, though substantial clinical data suggest the importance of brain metastases in the ALK+ NSCLC patient population.^{24,40}

The observed response rates were generally similar in our study to clinical trial results and, to a certain degree, even more favorable.^{28–30} However, in some cases these response rates differed significantly by the characteristics of the patients. Asian patients (vs non-Asian/non-White patients), former/passive/never smokers (vs current smokers), and patients with better functional status (vs patients with poorer functional status), all reported better response rates. Nevertheless, it should be noted that for all strata, response rates were objectively high and, due to small sample sizes, caution should be exercised when interpreting the comparisons across groups. Further, the RECIST criteria were not used to define response in this real-world study; rather, the oncologist determined response based on information in the patient’s chart.

Finally, the results suggest that alectinib was well tolerated in real-world clinical practice. Discontinuation was relatively uncommon over the study period (14%) and when it occurred it was mostly due to disease progression; no discontinuation due to adverse events was observed. Dosage reductions and dosage interruptions were even less common. Fatigue was the most common safety/tolerability event that led to dose modifications. However, it should be noted that the observation time for our study (due to the recent availability of alectinib) was less than that in clinical trials (14–20 months for randomized controlled trials vs 10 months for our study; Table 2).

Limitations

Most of the research questions were descriptive in nature, without clear threats to internal validity. However, the

method and the nature of the sample source may be a threat to the external validity. Only members of an Internet panel were eligible to join; these physicians (and, by extension, perhaps their patients) may differ from broader oncologist population. The selected panel did have a large representation with the intent to minimize this bias. Another threat to validity was the chart selection method. Although physicians were asked to select their most recent patients, physicians could have selected charts preferentially, which may have biased the sample of patients. Finally, the RECIST criteria were not used to determine response to treatment in this real-world study.

Conclusions

This retrospective chart review study is the first to document the real-world usage and clinical outcomes of patients with ALK+ NSCLC who are treated with alectinib after experiencing progression on crizotinib as their first ALK inhibitor. Substantial differences were observed between the real-world sample and the samples of alectinib clinical trials; our study suggested (consistent with other real-world data studies on ALK+ NSCLC patients more broadly^{31,32}) that patients using alectinib in clinical practice are older, more racially/ethnically and histologically diverse than those samples in published trials. Nevertheless, response rates are generally high and similar to those reported in clinical studies, though there is some variation by patient characteristics. In addition, alectinib was well tolerated in clinical practice with no discontinuations or dose interruptions and very few dose reductions due to adverse events.

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Disclosure

Marco D DiBonaventura was employed by Ipsos Healthcare at the time of the study and Bijal Shah-Manek is employed by Ipsos Healthcare, a health care consulting company. William Wong and Mathias Schulz are employed by Genentech (a subsidiary of Roche Holding AG). Mathias Schulz and William Wong hold shares from Roche Holding AG. The authors report no other conflicts of interest in this work.

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