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A phase II study of ^{18}F-fluorodeoxyglucose PET–CT in non-small cell lung cancer patients receiving erlotinib (Tarceva®); objective and symptomatic responses at 6 and 12 weeks

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ABSTRACT

Background: The aim of this study was to assess if ^{18}F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)–CT scanning could minimise the time non-responding patients were exposed to erlotinib (Tarceva®).

Methods: Patients were selected for clinical factors that would predict response to erlotinib. A FDG PET–CT and diagnostic contrast-enhanced (traditional) CT scan were carried out at baseline, and then a FDG PET–CT at 6 weeks and a traditional CT at 12 weeks were repeated. The primary end-point was rate of early progression in patients after 6 weeks, of which a minimum 12 out of 35 were required to make the study worthwhile. The responses at 6 (PET–CT) and 12 weeks (traditional CT) were compared and correlated with symptomatic response at both these time points.

Results: Forty seven patients were recruited with 38 and 33 patients assessable by FDG PET–CT at 6 weeks and traditional CT at 12 weeks, respectively. There was good correlation between Partial response (PR) at both time points and all 10 patients who had a PR at 12 weeks had a PR at 6 weeks. Of the 13 patients with progressive disease (PD) at 12 weeks, seven had PD at 6 weeks and could have had their treatment stopped early. No evaluable patient with stable disease (SD) (8/38) or PD (9/38) on FDG PET–CT at 6 weeks went on to have a later response. Symptomatic response at 6 or 12 weeks did not correlate well with objective response on scanning at either time point.

Conclusions: The primary end-point of this study was met as >12 (15/38) patients could have stopped treatment early on the basis of the FDG PET–CT scan result. A FDG PET–CT evaluable response of SD or PD at 6 weeks does predict future lack of response. No correlation was found between response and symptomatic response at either 6 or 12 weeks.

1. Background

The past decade has witnessed the evolution of novel agents which are targeted against receptors specifically involved in tumourogenesis. One of the most important of these receptors is the epidermal growth factor receptor (EGFR) and its associated tyrosine kinase.

Some clinical features such as female sex, never smoker, adenocarcinoma histology, and East Asian ethnicity have been noted to confer above-average response rates in trials

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in non-small cell lung cancer (NSCLC). The results of the IPASS study using gefitinib (Iressa®) suggests that the presence of a sensitising EGFR mutation can predict patients with a high chance of response to tyrosine kinase inhibitors and a patient without a mutation is best initially treated with chemotherapy.[1] Erlotinib is also most active in patients with an EGFR mutation, but even those patients without a documented mutation still have a survival benefit compared to placebo in both the second/third line setting (BR21 trial) and as maintenance after first line chemotherapy (SATURN trial).[2,3]

FDG PET, using a radioactive tracer analogue of glucose molecules labelled with 18-Fluorine (^{18}F 2-Fluoro-2-deoxy-D Glucose), is the commonest form of PET tracer used in nuclear medicine scanning for assessing malignant disease. PET and now PET/CT has a proven role in the staging of patients with lung cancer for radical treatment (surgery or radical radiotherapy).[4] The mean standard uptake value (SUV) measured during a PET examination and reported in numerical values is an independent prognostic factor in some, but not all, studies.[5,6]

Due to the functional element FDG PET–CT scanning is now being utilised to assess response to treatment in malignancies such as lymphoma, gastrointestinal stromal tumours, colorectal carcinomas and NSCLC. In one of the locally advanced NSCLC studies, there was poor agreement between PET and CT responses, before and after radiotherapy treatment, which were concordant in only 40% of patients.[7] A recent study on the radical treatment of oesophageal cancer used FDG PET–CT-assessed response 2 weeks after induction chemotherapy. The result of this examination was used to alter treatment and patients continued on the same chemotherapy if responding or switched straight to surgery if not. The trial suggested that this test leads to improved outcome compared to historical controls.[8]

Although PET has been used for some time in the assessment of response to neoadjuvant chemotherapy in NSCLC,[9] the reports of PET in the assessment of response to erlotinib are just beginning to appear. Zander and colleagues have evaluated 34 patients with untreated stage IV NSCLC and unknown mutational status with FDG PET uptake after 1 week (early) and 6 weeks (late) of erlotinib treatment and compared it to CT assessment after 6 weeks of treatment. Changes in FDG uptake after 1 week of therapy predicted non-progression after 6 weeks of therapy and patients with an early metabolic FDG response (cutoff value: 30% reduction in the peak SUV) had significantly longer survival.[10] In addition, a study of FDG PET–CT scans at baseline, 2 and 8 weeks after erlotinib, compared with diagnostic CT at baseline and 8 weeks has been recently reported in 74 erlotinib-treated patients, 51 of whom completed all imaging assessments. An early decrease in the SUV max was associated with improved survival.[11]

Symptomatic and quality of life (QOL) improvements are the challenging goal of lung cancer palliative treatments. In the randomised second/third line study, BR 21, erlotinib not only improved survival in previously treated patients with NSCLC, but also improves tumour-related symptoms (cough, dyspnoea and pain) and important aspects of QOL. We looked at the role of FDG PET–CT scanning in the assessment of early progression on erlotinib (as this is the only situation in which a tyrosine kinase inhibitor could be stopped) with PET at 6 weeks, and correlated this with the diagnostic CT data at 12 weeks. In addition, these early imaging responses were compared with symptomatic responses.

2. Patients and methods

2.1. *Eligibility*

Patients with histologically or cytologically confirmed diagnosis of stage IIIB/IV Non-Small Cell Lung Cancer (UICC staging 6th edition) were eligible for this study, with the following extra stipulations: (a) tumour had to overexpress EGFR i.e. $\geqslant$1% membrane staining on tumour cells via Dako IHC kit (cat no. K1492) or other standard EGFR testing, or have EGFR mutations documented; (b) patients without tissue available for EGFR testing, or who were EGFR negative, must demonstrate at least 2 of the following criteria: adenocarcinoma or bronchoalveolar histopathology, female sex, or never smokers (<100 in lifetime) were also eligible; (c) patients were able to receive erlotinib in situations where erlotinib would be considered an appropriate treatment whether it was in the first, second or third line settings.

Eligibility criteria also included the following: (a) patient must have recovered from any treatment related toxicities regardless of regimen prior to registration, except for alopecia, grade 1 fatigue or grade 1 neurotoxicity; (b) disease must be measurable on CT; (c) Age $\geqslant$18 years; (d) ECOG 0–2 and predicted life expectancy $\geqslant$12 weeks; (f) adequate haematopoietic, hepatic and renal function: absolute neutrophil count (ANC) $\geqslant 1.5 \times 10^9$/L and platelet count $\geqslant 100 \times 10^9$/L, bilirubin within or $\leqslant$1.5x upper limit of normal range (ULN), Alanine Transaminase (ALT) $\leqslant$2.5x ULN [or $\leqslant$5x ULN in cases of liver metastases], serum creatinine $\leqslant$1.5x ULN). Patients were not eligible if (a) they received concomitant CYP3A4 or CYP1A2 inducers/inhibitors which could impact significantly on their clinical care; (b) if they were receiving any concurrent anticancer, cytostatic or cytotoxic chemotherapy or had any other active malignancies unless deemed cured with at least 5 years of follow-up (*in situ* cervical cancer and *in situ*/basal cell skin cancer were permitted); (c) if they had active or uncontrolled infections, serious illnesses or medical conditions that could interfere with the patient's ongoing participation in the study; (d) if they had a history of psychiatric condition that might impair the patient's ability to understand or to comply with the requirements of the study or to provide informed consent; (e) if they had gastro-intestinal abnormalities, including inability to take oral medication, requirement for i.v. alimentation, active peptic ulcer or prior surgical procedures affecting absorption. Ability to lie flat for the duration of the PET/CT scan (for up to 50 min) was also a prerequisite. All patients gave written informed consent before screening of tissue for EGFR positivity, and those who fulfilled the trial entry criteria either by EGFR positivity or on clinical predictors were recruited. The study was conducted in accordance with the principle of good clinical practice, the declaration of Helsinki and was assigned EudraCT No. 2005-004508-35.

The primary end point of the study was the: (1) rate of early progression in patients after 6 weeks of erlotinib by PET/CT scanning. Secondary end-points were (1) comparison

of PET/CT findings at 6 weeks to diagnostic contrast enhanced CT scan at 12 weeks; (2) symptomatic response at 6 and 12 weeks compared to radiological findings. In addition, all responses to erlotinib were correlated to survival and duration of therapy and the different measures of SUV (mean and max baseline SUV, percentage change in 6 weeks of mean and max SUV) were correlated with objective findings.

On the basis that the response rate to these agents is of the order of 10%, and that 20% of patients have progressive disease at around 6–8 weeks, we expected to be able to diagnose progression earlier with PET/CT than with CT scanning. We predicted that about 40% of patients would show signs of progression on the PET/CT scan at 6 weeks and that consequently these patients would stop treatment at this time. If less than 20% of patients stopped treatment based on the results of the PET scan at 6 weeks, then the investigation would not be considered worthwhile and no better than standard tests. Using a single stage Phase II design, we aimed to recruit 35 evaluable patients. If 12 or more patients discontinued treatment at 6 weeks as a result of the scan, then the investigation would be considered to be a useful test and would be taken forward into further studies ($\alpha_{1\text{-sided}} = 5\%$; power = 80%).[12]

Baseline imaging was performed within 4 weeks prior to commencing erlotinib in all subjects. Any patient not completing their first 6 weeks of treatment within the initial 6-week assessment period was replaced until 35 patients had been recruited. All patients entered were described in the final report. Structural response by contrast enhanced CT was defined by Response Evaluation Criteria in Solid Tumours (RECIST) criteria version 1.0.

Metabolic response on PET/CT was defined by European Organisation for Research and Treatment of Cancer (EORTC) response criteria (Table 1).[13]

FDG PET/CT images were acquired using a Gemini 3D (Philips) PET-CT scanner. Patients were required to fast at least 4 h before the scan. ^{18}F-FDG (400 MBq) was injected intravenously if the blood sugar level was <10 mmol/l. Patients were rested for 60 min before PET acquisition. Emission data were acquired from the base of the skull to the upper thighs (4 min/bed; average, nine acquisitions). Unenhanced CT was performed from the base of the skull to the upper thighs for purposes of attenuation correction and image fusion for anatomical localisation (50 mAs, 50/slice).

2.2. *Imaging analysis of FDG uptake*

The primary PET outcome measures were the mean weighted SUV measured for tumours obtained during each of the scheduled FDG-PET/CT scans. The sum of all radioactive counts in all of the volumes of interest (VOI) representing all of the target lesions divided by the sum of all the voxels in all of the VOIs representing the target lesions is the SUV mean weighted average. The SUV mean was obtained by taking the sum of all counts in a VOI and dividing that number by the sum of all the voxels in the VOI. The SUV maximum (SUV max) measured the highest value in any voxel within a VOI. Analysis of PET/CT scan was performed without knowledge of other clinical studies.

The disease related symptoms categorised as fatigue, malaise, pain, cough, dyspnoea and haemoptysis, were all graded according to the CTCAE v3.0 at baseline, 6 and 12 weeks. Symptomatic response for all categories was defined as follows, (a) complete disappearance of symptoms (CR), (b) good improvement in symptoms (PR), (c) slight or no change in symptoms (NC), or (d) worsening of symptoms (PD). This methodology has been validated in previously published studies assessing the efficacy of chemotherapy in the resolution of lung cancer related symptomotology.[14,15]

3. Results

Forty seven patients were recruited between March 2006 and 2008 to give 38 analysable scans at 6 weeks and 33 patient/scans at 12 weeks. One patient did not have the FDG PET–CT

Table 1 – European Organisation for Research and Treatment of Cancer (EORTC) response definition.

Response	Definition	Masses
CR	Disappearance of all evidence of disease	(a) ^{18}F-fluorodeoxyglucose (FDG)-avid or PET positive prior to therapy: mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative: regression to normal size on CT
PR	Regression of measurable disease and no new sites	⩾25% decrease in tumour FDG uptake without evidence of new uptake. (a) FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative: regression on CT
SD	Failure to attain CR/PR or PD	<15% reduction or not >25% increase in tumour FDG uptake without evidence of new uptake. (a) FDG-avid or PET positive prior to therapy: PET positive at prior sites of disease and no new sites on CT or PET (b)Variably FDG-avid or PET negative: no change in size of previous lesions on CT
Relapsed disease or PD	Any new lesion or increase by ⩾25% of previously involved sites of tumour	Appearance of a new lesion(s) or ⩾25% increase in tumour FDG uptake

Based on the serial ^{18}F-FDG PET/CT studies, tumour response will be classified as CR (complete remission), PR (partial remission), SD (stable disease), and PD (progressive disease). Time to PD will be estimated using the date of the first treatment to the first evidence of disease progression.

Table 2 – Demographics.

Patients	47
Age	
Median (range)	63 (42–82)
Gender	
Male	18
Female	29
Diagnosis	
Squamous	6
Adenocarcinoma	28
Bronchio-alveolar	7
Poorly diff./NOS	6
Method of diagnosis	
Histology	42
Cytology	5
EGF expression on immunohistochemistry	
Positive	34
Negative	13
Smoking history	
Current smoker	5
Ex-smoker	22
Never smoked	20
Smokers: pack years	
Median and range	19.8 0.2–57
PS	
0	4
1	32
2	9
Time since diagnosis (months)	
Median and range	4.8 2.5–89.8
Treatment line	
First	34
Second	10
Third	3

scan at 6 weeks because of toxicity but did go on to have the CT scan at 12 weeks. Progressive disease was the commonest reason for patients being non-assessable at 6 weeks but 2 patients dropped out because of treatment toxicities.

Patient demographics are described in Table 2 and the study Consort diagram is shown in Fig. 1.

3.1. *FDG PET–CT responses*

The overall response rate at 6 weeks on FDG PET–CT was 32% (15/47). The overall PD rate at 6 weeks was 51% (24/47), counting every patient who did not get to 6 weeks as PD. Three patients stopped treatment because of reported toxicity and died shortly after. At 12 weeks the overall response rate was 23% (11/47) and PD rate was 55% (26/47).

Table 3 shows the correlation between the FDG PET–CT result at 6 weeks and the CT at 12 weeks. There was good correlation between PR at both time points and all 10 patients who had a PR at 12 weeks had a PR at 6 weeks. Progressive disease was reported on FDG PET–CT scanning in 9/38 evaluable patients at 6 weeks and on CT in 13/33 evaluable patients at 12 weeks. Two patients with SD at 12 weeks continued treatment for 136 (no symptomatic response) and 168 (symptomatic response) days, despite an increase in size of lesions by 10% and 15%, respectively. In other words, of the 13 patients

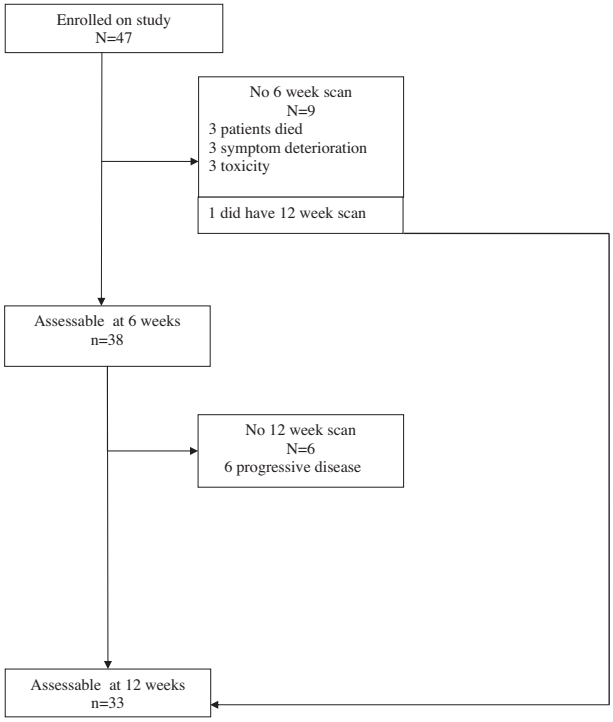

Fig. 1 – CONSORT diagram. Forty seven patients were recruited between March 2006 and 2008.

Table 3 – ^{18}F-fluorodeoxyglucose PET–CT at 6 weeks, response in vertical columns, CT at 12 weeks, response in horizontal rows.

PET–CT 6 week	CT 12 week					Total
	CR	PR	SD	PD	NE	
CR	1[a]					1
PR		10	2	2		14
SD			4	4		8
PD			2[b]	7	6	15
NE			1		8	9
Total	1	10	9	13	14	47

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

[a] Patient with mutation.

[b] Lasted 136 and 168 days and then PD.

with progressive disease (PD) at 12 weeks, seven had PD at 6 weeks and could have had their treatment stopped early. No evaluable patient with stable disease (SD) (8/38) or PD (9/38) on FDG PET–CT at 6 weeks went on to have a later response.

PET–CT responses were documented in 2/15 current smokers, 4/15 in ex-smokers and 9/15 in never smokers. In patients with squamous histopathology, 1/6 had a PR, 2/6 had SD and 3/6 had PD. In the seven patients with bronchoalveolar cancer, there were 1/7 PR, 4/7 SD and 2/7 PD. Interestingly, the single patient who had continual CR by PET/CT criteria and RECIST at 6 and 12 weeks, respectively was Asian and had an EGFR mutation.

PET–CT with SUV results at baseline and at 6 weeks were available for 35 patients (technical problems meant SUV

Table 4 – Standard uptake value mean and max changes correlation with response at 12 weeks on CT.

	Significance	Hazard ratio for 1 pt increase (or 100% change)	
Mean SUV pre-treatment	P = 0.2	1.13	(0.94:1.35)
Mean SUV at 6 weeks	P = 0.005	1.26	(1.07:1.48)
% Change in mean SUV	P = 0.001	9.49	(2.49:36.13)
Max SUV pre-treatment	P = 0.2	1.06	(0.97:1.14)
Max SUV at 6 weeks	P = 0.004	1.15	(1.05:1.26)
% Change in max SUV	P = 0.002	10.47	(2.46:44.67)

figures were not reported in three patients).The pre-treatment mean or SUV max values did not correlate with PET–CT at 6 weeks. However in an exploratory analysis (Univariate Cox regression analysis, Table 4) the 6 week mean and max values and the changes in both from baseline to 6 weeks were all significant predictors of survival.

There were 2/11 patients who did have an EGFR mutation and had a complete response (CR) and a PR as response at 6 weeks and long duration of treatment. Further tissue analysis from these subjects is ongoing.

3.2. *Symptomatic responses*

Symptomatic response was a secondary end-point in this study and the correlation with FDG PET–CT response at 6 weeks is shown in Table 5. The one patient with an objective CR reported no improvement at 6 weeks. Symptomatic responses were documented in 10/14 responders on PET–CT but one responding patient had no change in symptoms and three felt worse. Of the nine patients with NC as an objective response four felt better, two NC and two felt worse. Of the 16 patients with PD on FDG PET–CT, three described improvement, five no change and seven progressive symptoms. At 12 weeks things were no clearer except the one patient with a CR did have resolution of symptoms (Table 6).

Table 5 – ^{18}F-fluorodeoxyglucose PET–CT at 6 weeks response in vertical columns, symptomatic response at 6 weeks response in horizontal rows.

PET 6 week	Symptoms 6 week				Total
	PR	NC	PD	NE	
CR		1			1
PR	10	1	3		14
SD	4	2	2		8
PD	3	5	7		15
NE	1	0	3	5	9
Total	18	9	15	5	47

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

Table 6 – CT at 12 weeks response in vertical columns, symptomatic response at 12 weeks response in horizontal rows.

CT 12 week	Symptoms 12 week					Total
	CR	PR	NC	PD	NE	
CR	1					1
PR	1	7	2			10
SD		3	5		1	9
PD	1	2	3	4	3	13
NE					14	14
Total	3	12	10	4	18	47

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

3.3. *Survival*

Survival was calculated from the date erlotinib commenced to death or date of last follow-up. The survival curves show that

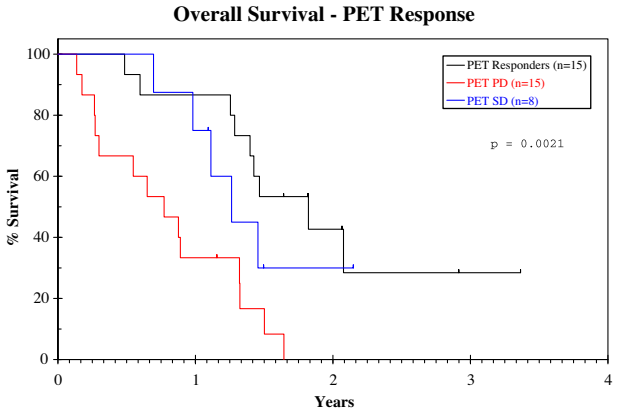

Fig. 2 – Overall survival according to ^{18}F-fluorodeoxyglucose PET–CT response.

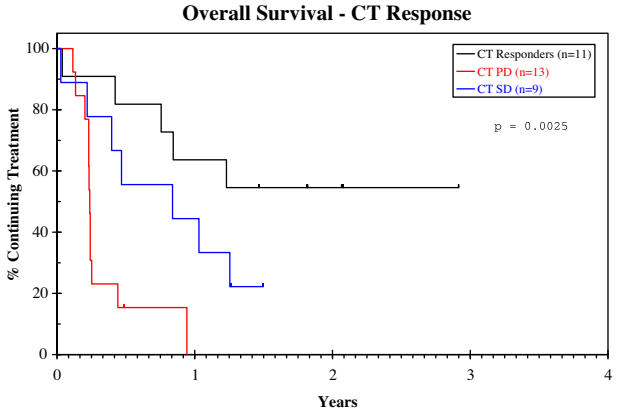

Fig. 3 – Overall survival according to CT response at 12 weeks.

responders live longer than SD which was better than progressive disease on both PET–CT scan (Fig. 2) and CT scan (Fig. 3).

3.4. *Toxicity*

There were three episodes of grade 3 rash, two episodes of grade 3 diarrhoea, four episodes of grade 3 fatigue and one case of grade 3 interstitial pneumonitis which was not reversible and not progressive. There was no grade 4 toxicity.

4. Discussion

This study was planned and executed at a time when the information on the importance of the presence of an EGFR sensitising mutation was less widely accepted than it is nowadays. The primary end-point for this trial was met in that the FDG PET–CT scan at 6 weeks proved to be an appropriate test as at least 12 or more patients could have stopped their treatment at that time-point because of progressive disease. No patient who had SD or PD on FDG PET–CT at 6 weeks, later went on to have a response. The 6 week time point would appear to be a practical time to look for early progression in erlotinib treated patients.

The overall response rate at 6 weeks on FDG PET–CT was 32% (15/47) which is higher than expected for a group of patients selected on clinical characteristic and not selected for EGFR mutation status. However, it was an enriched population with the majority of patients being either female, with adenocarcinoma, either former or never smokers and with EGFR overexpression on immunohistochemistry and in more than 70% (34/47) the treatment setting was first-line. In the randomised second/third line study, BR 21, erlotinib improved overall survival in previously treated patients with NSCLC and EGFR status confirmed by IHC correlated with response.[2] On multivariate analysis, the response rate was higher in patients with EGFR positivity on immunohistochemistry than those who were negative (11% versus 4%). Based on this, we used clinical and immunohistochemical criteria (but not mutation status) for the selection of patients to receive erlotinib.

Alongside the survival advantage conferred by erlotinib, the BR21 study confirmed improved tumour-related symptoms and important aspects of QOL. In this study we have also assessed symptomatic response on the basis that it may be as good as imaging in deciding whether a patient benefits from continued treatment in this palliative setting. However, symptom response at 6 and 12 weeks was not reliable in assessing early progression. Patients receiving oral therapy with a lack of therapeutic options coupled with a poor prognosis are likely to describe a significant placebo response.

While we could recommend further work on earlier PET scanning e.g. at 4 weeks and a separate study with early FDG PET–CT in patients with mutations, from this study a scanning test at 6 weeks and in particular a FDG PET–CT is useful in making decisions about discontinuing treatment in patients with NSCLC receiving erlotinib. We would not recommend reliance on patient reported symptoms response.

Conflict of interest statement

Both Dr. O'Brien and Dr. Popat have acted on behalf of Roche on advisory boards and consultancy positions. In addition, Roche have provided honoraria for both these roles and travel subsidies for international conferences.

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