Improvements in Quality of Life and Disease-related Symptoms in Phase I Trials of the Selective Oral Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor ZD1839 in Non-Small Cell Lung Cancer and Other Solid Tumors

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ABSTRACT

Purpose: The feasibility and utility of assessing quality of life (QoL) and disease-related symptoms in patients with advanced cancer have been evaluated in two Phase I clinical trials of p.o. administered ZD1839 (‘Iressa’), an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced cancer.

Experimental Design: Functional Assessment of Cancer Therapy (FACT) questionnaires, including disease-specific subscales for lung, head and neck, colorectal, prostate, and ovarian cancer, were completed by patients in two open-label, Phase I, escalating multiple-dose safety and tolerability trials.

Results: In 157 patients, 92% of whom had received prior therapy, compliance in returning FACT questionnaires was 87% (European/Australian trial) and 57% (United States trial). This did not appear to be influenced by dose level or tumor type. For patients with colorectal, prostate, or ovarian cancer, median QoL [FACT and Trial Outcome Index (TOI)] scores deteriorated over time. In contrast, for patients with non-small cell lung cancer (NSCLC) or head and neck cancer, median FACT and TOI scores did not deteriorate significantly, and in the United States trial, head and neck cancer scores improved significantly over time. In patients with NSCLC, symptom-related scores measured by the Lung Cancer Subscale of FACT-L appeared sensitive to clinical change.

Conclusions: QoL (FACT-L) questionnaires were used successfully in the Phase I clinical trials of ZD1839. They appeared to be a sensitive tool to monitor clinical changes for the five tumor types in these trials and showed that ZD1839 has the potential to improve patients’ QoL.

INTRODUCTION

With the increasing clinical use of anticancer agents with new modes of action, new measures of efficacy are needed to quantify clinical benefit. Many novel agents combine reduced toxicity with predicted mechanistic effects, such as decreased or delayed tumor growth, and often give lower tumor response rates than traditional therapies. Trial end points such as time-to-disease progression, QoL, and duration of symptom stabilization or improvement, generally considered from regulatory and clinical viewpoints to be of secondary importance in trials of cytotoxic agents, may consequently be of higher importance in trials of many novel agents (1). Patient-reported health-
related QoL is increasingly being used in symptomatic patients with advanced cancer as a tool for assessing symptom relief and treatment efficacy.

Early studies by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) showed that it is possible to successfully implement health-related QoL assessments within clinical trials of anticancer agents. Compliance rates for completing questionnaires were high, with a minimal amount of missing data (2). Such studies allowed the NCIC CTG to gather data showing that QoL scores at baseline are an independent prognostic variable in a general population of cancer patients receiving chemotherapy; for example, patients with high QoL lived significantly longer than patients with low QoL (3). Several other suitable tools have been developed for patients with cancer, including the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (4–6), the Functional Living Index—Cancer (FLIC; Ref. 7) and the Cancer Rehabilitation Evaluation System (CARES; Ref. 8). However, tools such as these often measure different aspects of QoL; some take account of disease-related symptoms, whereas others may place more emphasis on general concerns such as increased anxiety or reduced mobility. Direct comparison of results obtained with different tools is therefore difficult (9–11).

In Phase I trials of ZD1839 (‘Iressa’), a selective EGFR-tyrosine kinase inhibitor that disrupts signaling pathways important in tumor growth (12), the FACT series of questionnaires were used. FACT instruments, designed to be sensitive to change in cancer patients, are simple to use and score. They contain questions designed to measure SWB and EWB as well as PWB and FWB (13). In all, 27 questions make up the FACT-G tool, and each item is rated on a 5-point scale from 0 (not at all) to 4 (very much). The four general measures of well-being are complemented with a fifth scale that is specific to the patient’s disease (Fig. 1). FACT subscales that allow the assessment of disease-related symptoms associated with specific tumor types were available for the five tumor types studied in Phase I trials of ZD1839 as follows: FACT-L for NSCLC (14) and FACT-HN for head and neck (15–17), FACT-C for colorectal (18), FACT-P for prostate (19), and FACT-O for ovarian (20, 21) cancers. To assess overall QoL, the full FACT score (the FACT-G total plus the disease-specific subscale total) is used.

FACT-L and its LCS (14) have been validated as means of assessing improvements in the disease-related symptoms of lung cancer. These include cough, breathlessness, fatigue, loss of appetite, weight loss, chest pain or discomfort, constipation, and poor sleep (14, 22). Analysis of data from the Eastern Cooperative Oncology Group study 5592, a randomized trial comparing three chemotherapy regimens in 599 patients with advanced NSCLC, showed that changes in LCS score were related to established clinical indicators, such as objective tumor response and time to progression, and that the minimum clinically meaningful change was not likely to be less than 2 points on the LCS (22).

An additional measure of QoL provided by the FACT instrument is the TOI. TOI is the sum of the PWB, FWB, and disease-specific subscale scores. TOI has also been shown to be sensitive to chemotherapy (23, 24) and to established clinical indicators such as time to progression (22).

This report principally focuses on QoL and symptom measures applied to two Phase I studies that were undertaken to establish the safety and tolerability of ZD1839 given p.o. for 28 consecutive days to patients with defined, advanced tumors. These trials showed ZD1839 to be well tolerated with evidence of activity in several tumor types; the results are reported in detail elsewhere (25–27). Here we evaluate the feasibility and sensitivity of evaluating QoL and symptoms with the relevant FACT questionnaires in the patient populations treated with ZD1839 in these trials.
MATERIALS AND METHODS

Trial Design. These were open-label, Phase I, sequential block, dose-escalation trials, one carried out at six centers in the United States (trial 11), the other at ten centers in Europe and Australia (trial 12). The studies were undertaken to establish the safety and tolerability of ZD1839 in patients with one of five defined, advanced tumor types, and additionally to determine the pharmacokinetic profile and to further explore the dose-related biological effects on tumor growth and patient benefit.

Patient Eligibility. Patients were required to have histological/cytological confirmation of metastatic or advanced NSCLC, head and neck, prostate, ovarian or colorectal cancer, refractory to conventional chemotherapy or for which no effective therapy existed. EGFR expression status was not used as a criterion for inclusion or exclusion. Patients were aged ≥18 years, with a WHO performance status of 0 or 1, and they gave written informed consent in accordance with the requirements of the ethics committee at each center.

Treatment. ZD1839 was administered p.o., twice on day 1 and daily thereafter for contiguous 28-day cycles. The ZD1839 dose levels to be investigated were 150, 225, 300, 400, 600, 800, and 1000 mg/day, and dose escalation proceeded to the highest level at both trials.

QoL. QoL was assessed using the FACT series of disease-specific questionnaires: FACT-L (maximum score, 136), FACT-HN (maximum score, 152), FACT-O (maximum score, 156), FACT-C (maximum score, 144), and FACT-P (maximum score, 144). Questionnaires were self-administered, taking about 8 min to complete. All of the questionnaires had been previously validated with respect to their psychometric properties and sensitivity to clinical changes. The following scores were calculated from the FACT questionnaires and listed by patient: the PWB, FWB, SWB, and EWB scores, the disease-specific subscale score (LCS, head and neck, colorectal, ovarian, and prostate cancer subscales), and the overall score. In addition, the TOI (the sum of PWB, FWB, and disease-specific subscale scores) was calculated (14–19, 21).

FACT questionnaires were completed at baseline, on days 14 and 28 of the first treatment period, then on day 28 of each treatment period, before clinical assessment, and before patients were informed about the status of their disease, and at withdrawal, when a final QoL questionnaire was completed. The best overall scores for the TOI and FACT total were based on individual visit responses. Responses were categorized as follows: “improved,” two visit responses of improved a minimum of 28 days apart, with no interim visit reports of worsened; “no change,” two visit responses of no change or improved a minimum of 28 days apart, with no interim visit reports of worsened; “worsened,” two consecutive visit responses of worsened; and “other,” none of the above. For TOI and FACT-L, responses of improved, worsened, or no change were defined as score changes of ≥ +6, ≤ −6, or between these values, respectively; this degree of change has been shown to be clinically meaningful for FACT-L (22). A 6-point change in FACT-HN was also used to define clinically meaningful change in the head and neck tumor patients, although its clinical relevance has not yet been fully documented.

Monitoring Disease Symptoms in Patients with NSCLC

Using the LCS. Of the nine items in the disease-specific section of FACT-L, seven allow quantitation of symptoms and are totaled to give the LCS score. LCS scores, therefore, range from 0 (fully symptomatic) to 28 (asymptomatic). In patients with NSCLC, disease-related symptoms were measured weekly: patients completed a diary card recording the severity of LCS symptoms on days 8, 15, and 22 of each 28-day cycle. The LCS was also evaluated within the full FACT-L questionnaire every 28 days. Patients were considered to be evaluable for symptom improvement if they had a baseline LCS score of ≤24 of a possible 28. For the LCS, responses of “improved,” “worsened” or “no change” were defined as score changes of ≥ +2, ≤ −2, or between these values, respectively, sustained for ≥4 weeks (a 2–3-point worsening in LCS score from baseline to 12 weeks has been shown to be associated with early progression (22) and is, therefore, regarded as being clinically meaningful). This information was used to determine the symptom-related end points including clinical symptom improvement rate and time to symptom improvement.

Antitumor Activity. Baseline tumor assessment by imaging or radiography was performed no more than 14 days before the start of the trial. The extent of disease was assessed at day 28, and monthly until withdrawal, using RECIST criteria. Patients with partial response or stable disease remained on study in the absence of toxicity.

RESULTS

Patients and Antitumor Activity

In total, 157 patients were treated: 69 in the United States trial and 88 in the European/Australian trial. Patients had one of five tumors: NSCLC, head and neck, colorectal, prostate, or ovarian (Table 1). Most patients had a performance status of 1, and both patient populations were heavily pretreated (Table 1).

Table 2  Patients who remained on study for ≥6 months (≥6 × 28-day treatment periods)

<table>
<thead>
<tr>
<th>ZD1839, mg/day</th>
<th>No. of patients</th>
<th>Tumor</th>
<th>Time on study (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 (n = 6)</td>
<td>1</td>
<td>NSCLC</td>
<td>17</td>
</tr>
<tr>
<td>225 (n = 14)</td>
<td>1</td>
<td>NSCLC</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>HRPC</td>
<td>7b</td>
</tr>
<tr>
<td>300 (n = 14)</td>
<td>1</td>
<td>NSCLC</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Ovarian</td>
<td>9e</td>
</tr>
<tr>
<td>400 (n = 14)</td>
<td>1</td>
<td>Colorectal</td>
<td>6</td>
</tr>
<tr>
<td>1000 (n = 12)</td>
<td>1</td>
<td>HRPC</td>
<td>6d</td>
</tr>
</tbody>
</table>

European/Australian study
150 (n = 13) | 1 | NSCLC | 15
225 (n = 13) | 2 | Head and neck | 8, 28+ \textsuperscript{f}
300 (n = 13) | 1 | Head and neck | 9
               | 1 | NSCLC | 8
400 (n = 13) | 1 | Colorectal | 6
               | 1 | Head and neck | 14f
               | 1 | NSCLC | 6
               | 1 | Ovarian | 7f
600 (n = 6) | 2 | NSCLC | 25, 14f
800 (n = 6) | 1 | NSCLC | 7
1000 (n = 5) | 1 | NSCLC | 8f

United States study

a HRPC, hormone-resistant prostate cancer.
\textsuperscript{b} Patient had sustained decrease from baseline prostate-specific antigen (PSA) >50% over 4 months.
\textsuperscript{c} No change in CA125.
\textsuperscript{d} Worsening in PSA levels observed.
\textsuperscript{e} Partial response.
\textsuperscript{f} Includes time spent on extension trial 0026.
\textsuperscript{g} Patient had a 48% reduction in serum CA125.

In the European/Australian trial, of 92 patients enrolled, 88 received at least one dose of ZD1839 and were evaluable for safety, and 58 patients were evaluable for efficacy. Of 71 patients enrolled in the United States trial, 69 received at least one dose of ZD1839 and were evaluable for safety, and 58 patients were evaluable for efficacy. Patients were recruited at one dose of ZD1839 and were evaluable for safety, and 58 patients were evaluable for efficacy. Of 71 patients, including 10 with NSCLC (one with a partial response), fell into this category (Table 2).

Compliance
In the European/Australian trial, overall compliance with QoL questionnaires was >77% at all time points, and all forms received were evaluable (Table 3). Neither dose level nor tumor type appeared to influence the compliance rate. In the United States trial, patients with NSCLC and head and neck cancer received the largest number of questionnaires and overall questionnaire completion rates for these patients were 55 and 52%, respectively (Table 3). The compliance rate was relatively low compared with the European/Australian trial, primarily because of administrative issues: a number of questionnaires were poorly completed and could not be associated with individual patients, and data were unavailable from one center. Compliance rates increased after baseline and were highest for assessments recorded after the first treatment period. After this time, compliance appeared to diminish, again due to administration issues. Overall compliance approximated to that at baseline and was similar to levels in comparable published studies (e.g., Refs. 28 and 29).

QoL
European/Australian Trial. Median changes from baseline in FACT QoL scores are summarized in Table 4. For patients with prostate and ovarian cancer, median QoL scores (as measured by both FACT and TOI) deteriorated over time. However, for patients with head and neck, NSCLC, and colorectal cancer, median QoL scores did not show any clinically meaningful deterioration over the time period measured, and patients with NSCLC who remained on study for more than 3 months sustained a median improvement in FACT-L score of 1.7. A change of 6 points compared with baseline is considered to be clinically significant for FACT-L (22), and the range of scores from −27.6 to +17.0 encompasses several patients whose scores were improved by ≥6. In view of the antitumor activity seen in terms of a time on study of ≥6 months in several patients with NSCLC (Table 2), this is strong evidence that FACT-L was sensitive to clinical changes in individual patients.

United States Trial. Overall, the median changes from baseline in total FACT scores for the groups of patients with head and neck cancer and NSCLC were 7.0 and 2.0, respectively (Table 5). This represents an improvement in QoL for the group of patients with head and neck cancer, and a slight improvement for the group of patients with NSCLC. These median total FACT scores reflect the clinical stability of patients remaining on study for ≥6 months. The change in median TOI score from baseline ranged from −6.0 for patients with colorectal cancer to +2.8 for patients with head and neck cancer (Table 5). With the TOI system, the overall results indicated that there was no median change in QoL for the group of patients with head and neck cancer or NSCLC. TOI scores indicated worsening in QoL for patients with colorectal, ovarian, and prostate cancers after 3 or more months; however, patient numbers were too small for conclusions to be drawn for these groups.

Five of 18 individual patients with head and neck cancer completed FACT-HN questionnaires at baseline and over a period lasting 1 month or more (including four patients who remained on study for ≥6 months (Table 2). During this period, one patient improved (≥6-point increase) compared with baseline, two patients did not change, and two had a 6-point reduction. These findings were mirrored by TOI scores: one patient had at least a 6-point improvement, two experienced no change, and two had a 6-point reduction.

Nine of 39 individual patients with NSCLC completed a baseline assessment and remained on study for at least 1 month. Of these, one had an improvement (≥6-point increase) sustained for at least 1 month, five experienced no change, and three had a 6-point reduction. One of the patients (on 600 mg/day ZD1839) who remained on study for ≥6 months had a sustained improvement from baseline in FACT-L score and TOI of 30 points for ~10 months. In addition, five patients (on doses of ZD1839 ranging from 150 to 1000 mg/day) had no change (<6-point reduction) in FACT-L compared with baseline. Four of these also had no change in TOI. The three patients who experienced a 6-point reduction in FACT-L score withdrew...
because of disease progression after 1–2 months. These three patients, plus one of the patients with no change in FACT-L score, had a reduction in TOI of ≥6 points.

In summary, FACT-HN and FACT-L, along with the TOI for both tools, appeared sensitive to clinical change in patients with head and neck cancer and with NSCLC, respectively.

LCS

**European/Australian Trial.** The median baseline LCS score for the 22 patients with NSCLC was 19.5, indicating that these patients were symptomatic. Individual baseline LCS scores ranged from 14 (one patient, the most symptomatic) to 25 (two patients, the least symptomatic). Thirteen of the 22 patients with NSCLC were assessed for symptom changes using the LCS. As shown in Table 6, median overall change from baseline for LCS was 0.5 (range, −9.0 to + 8.0). FACT-L, TOI, and LCS data from the European/Australian trial are summarized in Table 7, showing a score of “improved” or “no change” in the majority of patients. Three of these patients remained on study for ≥ 6 months: one (on 150 mg/day ZD1839; Table 2) for 14 months, and two (one on 225 mg/day and one on 300 mg/day) for 17 and 6 months, respectively (Table 2). Plots of LCS scores for the duration of treatment of these patients (Fig. 2) illustrate that symptoms were relatively stable throughout the time on study for all three patients. Of the remaining 10 patients with NSCLC for whom post-baseline assessments are available (all withdrew because of disease progression), the best overall LCS response was “improved” in three patients, a response sustained for 10, 6 months, respectively (Table 2). Plots of LCS scores for the duration of treatment of these patients (Fig. 2) illustrate that symptoms were relatively stable throughout the time on study for all three patients. Of the remaining 10 patients with NSCLC for whom post-baseline assessments are available (all withdrew because of disease progression), the best overall LCS response was “improved” in three patients, a response sustained for 10,
Table 5  Change from baseline in FACT QoL questionnaire and TOI for all of the registered patients in the United States trial (a positive score change denotes improvement)

<table>
<thead>
<tr>
<th>No. of 28-day treatment periods</th>
<th>NSCLC (n = 39)</th>
<th>Head and neck (n = 18)</th>
<th>Colorectal (n = 7)</th>
<th>Prostate (n = 3)</th>
<th>Ovarian (n = 2)</th>
<th>Total (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>7.0</td>
<td>-4.3</td>
<td>-0.6</td>
<td>-4.3</td>
<td>2.0</td>
</tr>
<tr>
<td>Range</td>
<td>-32.2 to 35.3</td>
<td>-25.0 to 18.0</td>
<td>-17.0 to 6.0</td>
<td>-23.8 to 6.0</td>
<td>-32.0 to 8.5</td>
<td>-32.2 to 35.3</td>
</tr>
<tr>
<td>n</td>
<td>52</td>
<td>37</td>
<td>9</td>
<td>10</td>
<td>17</td>
<td>125</td>
</tr>
<tr>
<td>≤1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>-4.1</td>
<td>0.9</td>
<td>-3.7</td>
<td>3.0</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Range</td>
<td>-3.2 to 26.5</td>
<td>-25.0 to 9.0</td>
<td>-4.8 to 6.0</td>
<td>-0.2 to 6.0</td>
<td>-8.0 to 8.5</td>
<td>-32.2 to 26.5</td>
</tr>
<tr>
<td>n</td>
<td>16</td>
<td>12</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>37</td>
</tr>
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<td>2 to 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.3</td>
<td>5.8</td>
<td>-2.6</td>
<td>-3.0</td>
<td>-2.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Range</td>
<td>-25.7 to 32.3</td>
<td>-12.0 to 10</td>
<td>-17.0 to 5.0</td>
<td>-11.6 to 5.0</td>
<td>-13.0 to 6.4</td>
<td>-25.7 to 32.3</td>
</tr>
<tr>
<td>n</td>
<td>10</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>&gt;3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3.1</td>
<td>11.0</td>
<td>-6.0</td>
<td>-12.4</td>
<td>-6.7</td>
<td>7.2</td>
</tr>
<tr>
<td>Range</td>
<td>-12.7 to 35.3</td>
<td>-1.0 to 18.0</td>
<td>-6.0 to -6.0</td>
<td>-23.8 to -1.0</td>
<td>-32.0 to -7.6</td>
<td>-32.0 to 35.3</td>
</tr>
<tr>
<td>n</td>
<td>26</td>
<td>19</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td>Overall TOI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.0</td>
<td>2.8</td>
<td>-6.0</td>
<td>-1.5</td>
<td>-4.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Range</td>
<td>-32.0 to 31.5</td>
<td>-16.0 to 8.0</td>
<td>-19.0 to 6.0</td>
<td>-25.0 to 5.0</td>
<td>-22.0 to 5.5</td>
<td>-32.0 to 31.5</td>
</tr>
<tr>
<td>n</td>
<td>54</td>
<td>37</td>
<td>9</td>
<td>10</td>
<td>17</td>
<td>127</td>
</tr>
</tbody>
</table>

*a n, number of forms received.

Table 6  Change from baseline in LCS score for all of the registered patients in the European/Australian trial and the United States trial (a positive score change denotes improvement)

<table>
<thead>
<tr>
<th>No. of 28-day treatment periods</th>
<th>European/Australian trial</th>
<th>United States trial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>overall</td>
<td>≤1</td>
<td>2 or 3</td>
</tr>
<tr>
<td>Median</td>
<td>0.5</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Range</td>
<td>-9.0 to 8.0</td>
<td>-5.0 to 5.2</td>
<td>-6.0 to 8.0</td>
</tr>
<tr>
<td>n</td>
<td>94</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
<td>-0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Range</td>
<td>-9.0 to 24.5</td>
<td>-9.0 to 22.5</td>
<td>-4.0 to 23.5</td>
</tr>
<tr>
<td>n</td>
<td>53</td>
<td>18</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 7  Best overall responses in FACT-L, TOI, and LCS scores in patients with NSCLC in the European/Australian trial

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>FACT-L</th>
<th>TOI</th>
<th>LCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>No change</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Worsened</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Missing dataa</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

*a Includes those who had data but did not qualify for the above categories.

14, and 24 weeks, respectively; whereas two patients showed “no change” in LCS response and remained on therapy for 8 and 2 weeks (Fig. 3). The LCS response of “worsened” was seen in five patients, four of whom remained on ZD1839 therapy for ≤2 months.

United States Trial. The LCS demonstrated an overall median change from baseline of 1.0 (not clinically meaningful) for patients with NSCLC (Table 5). Six of the seven patients with a time on study of ≥6 months (Table 2) were evaluable for FACT-L. Two (on 600 and 800 mg/day ZD1839) had sustained improvements in LCS (≥2 points) for about 10 months and 5 months, respectively. Four other patients (on 150-1000 mg/day ZD1839) with a time on study of ≥6 months had a score of “no change” for periods of 2–8 months.

DISCUSSION

For the successful gathering of QoL data, a high degree of cooperation between clinical trial investigators, nurses, data managers, and central office administrative staff, as well as a wide awareness of the trial policy and methods of measuring QoL, are ideally needed (2). Therefore, when a drug has the potential for a positive effect on QoL, it is sensible to begin QoL monitoring in Phase I trials, both to allow evaluation of the tool in question and to gain experience in its administration. Taken together, these Phase I trials of ZD1839 showed encouraging results for the use of the FACT tool in monitoring QoL in patients with advanced cancer. Levels of compliance, although substantially higher in the European/Australian trial than in the
United States trial, were satisfactory for both trials and were comparable with other published studies of QoL in patients with similar cancers in which FACT questionnaires were used (e.g., the studies in Refs. 28 and 29).

Results show that FACT questionnaires for NSCLC and head and neck, prostate, colorectal, and ovarian cancer were sensitive to clinical change (e.g., time on study as a surrogate for disease control) in patients receiving trial medication. Median QoL scores for patients with NSCLC or head and neck cancer in both trials, and also for patients with colorectal cancer in the European/Australian trial, showed no significant deterioration. Moreover, in the case of head and neck cancer in the United States trial, QoL scores improved significantly (the median FACT score for 18 patients treated with ZD1839 increased by 7 points).

When patients were stratified according to antitumor activity, which was seen predominantly in patients with NSCLC and to various degrees in all of the tumor types in the trial, additional patterns emerged in QoL response. Patients with NSCLC showing disease control (in the form of a time on study of ≥6 months) tended to have improvement or stabilization of specific disease-related symptoms (LCS scores) over the treatment period before progression. Therefore, the beneficial effects of ZD1839 seem to be measurable using LCS, and, when a change in LCS score of 2 points was taken as being clinically meaningful (22), it was possible to identify symptom responses to ZD1839. In cases in which ZD1839 did not seem to induce tumor control (in the form of a time on study of ≥6 months), LCS scores worsened rapidly in some patients, although patients within this group who remained on study for a relatively long period tended to show a best LCS response of “no change” or “improved.” The observed association between disease control and symptom improvement raises the possibility that LCS could be used as a primary measure of efficacy in patients with symptomatic advanced malignancy, because it could potentially be more clinically meaningful than reporting a response rate.

To investigate other potential surrogate markers of efficacy in these trials, pharmacodynamic studies on patient skin biopsies were also carried out. Immunohistochemical analysis, reported elsewhere (30), showed that significant inhibition of activated (phosphorylated) EGFR and significant changes in marker molecules of downstream effect were seen in the normal skin of patients during treatment with ZD1839, at dose levels well below that causing unacceptable toxicity. Additional studies are...
needed to assess whether skin effects can be used to monitor antitumor activity.

In summary, many of the patients treated with ZD1839 in these two Phase I trials had improvements in disease-related symptoms that translated into QoL benefits [wider results of these trials are published elsewhere (25–27)]. In the case of patients with NSCLC, for whom LCS data (presented in detail for one of the trials) provides a validated measure of symptom relief, improved or stable symptoms were seen in patients with disease control defined by a time on study of ≥6 months. Improved or stable symptoms were seen in a significant number of patients even in the absence of disease control. Overall, the data are consistent with the idea that ZD1839 can offer improved QoL in patients with NSCLC. In addition, patients with NSCLC or head and neck cancer showed stable or improved median QoL scores when treated with ZD1839. In patients with all five tumor types, there appeared to be an association between symptom improvement and disease control, and symptom improvement was associated with increased time on study.

The QoL data presented here support the use of FACT questionnaires as part of the evaluation of ZD1839 efficacy. Recently, data from Phase II trials of ZD1839 monotherapy in patients with advanced, previously treated NSCLC, in which the monitoring of QoL and symptom improvement using FACT-L and LCS was an important end point, have been reported. Results showed sustained improvements in disease-related symptoms in patients with disease control, defined as complete response plus partial response plus stable disease (31–34). In addition, recent data show that ZD1839 has antitumor activity against head and neck cancer: in a Phase II study in which 40 patients were evaluable for response, 8 (20%) had an objective response, and 14 (35%) had stable disease. Of these, 8 patients remained on the drug for up to 7 months (35). These data further support our conclusion that ZD1839 has the potential to offer clinically significant benefits in symptom improvement and QoL in heavily pretreated patients with advanced NSCLC, head and neck cancer and other tumor types.

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Improvements in Quality of Life and Disease-related Symptoms in Phase I Trials of the Selective Oral Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor ZD1839 in Non-Small Cell Lung Cancer and Other Solid Tumors

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