Phase II study of axitinib with doublet chemotherapy in patients with advanced squamous non–small-cell lung cancer

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ABSTRACT <<Word limit, 350; word count, 249 >>
Background: Axitinib is an orally active and potent tyrosine kinase inhibitor of vascular endothelial growth factor receptors 1, 2 and 3. This phase II study assessed the efficacy and safety of axitinib combined with cisplatin/gemcitabine in chemotherapy-naïve patients with advanced/metastatic (stage IIIB/IV) squamous non–small-cell lung cancer (NSCLC).

Methods: Axitinib (starting dose 5 mg twice daily [bid]; titrated up or down to 2–10 mg bid) was administered orally on a continuous schedule with cisplatin (80 mg/m² intravenously [i.v.] every 3 weeks) and gemcitabine (1,250 mg/m² i.v. on days 1 and 8 of each 3-week cycle), and was continued as monotherapy after completion of six cycles (maximum) of chemotherapy.

Results: Of the 38 patients treated, one (2.6%) patient achieved a complete response and 14 (36.8%) patients had a partial response; nine (23.7%) patients showed stable disease and three (7.9%) patients had disease progression. Median progression-free survival was 6.2 months, and median overall survival was 14.2 months. The probabilities of 12-month and 24-month survival were 63.2% and 30.8%, respectively. The most frequent grade ≥3 toxicities were neutropaenia and hypertension (13.2% each). Three (7.9%) patients experienced haemoptysis, of which one case (2.6%) was fatal.

Conclusions: Treatment with the combination of axitinib and cisplatin/gemcitabine demonstrated anti-tumour activity in patients with advanced/metastatic squamous NSCLC and the fatal haemoptysis rate was low. However, without a reference arm (cisplatin/gemcitabine alone), it is not conclusive whether the combination is better than chemotherapy alone. This
study was registered at ClinicalTrials.gov, registration # NCT00735904, on
August 13, 2008.

**Keywords:** Non–small-cell lung cancer, squamous cell, axitinib, anti-angiogenic
treatment, platinum-based chemotherapy, phase II

**INTRODUCTION**

Non–small-cell lung cancer (NSCLC), a heterogeneous group of histologies that
includes adenocarcinoma, squamous cell carcinoma and large cell carcinoma,
accounts for approximately 85% of all lung cancers [1]. Patients with NSCLC
typically present with locally advanced or metastatic disease at the time of
diagnosis [2], and in these cases prognosis is poor, with a 5-year survival rate of
less than 10% [3].

Platinum-based double-agent chemotherapy, which is standard first-line
treatment for most patients with stage IIIB or IV NSCLC, is associated with an
objective response rate of 17–38% and a median survival time of approximately 7
to 14 months [4-10]. Clinical evidence indicates that there are minimal differences
in efficacy (objective response rate and overall survival) between the various
platinum-based doublet regimens in the treatment of advanced NSCLC [11,12],
and that the addition of a third cytotoxic agent increases toxicity but does not
prolong survival [13]. Thus, it would appear that standard cytotoxic chemotherapy
has reached a therapeutic plateau in advanced NSCLC [14]. As a consequence,
current research is focused on addition of a molecularly targeted anti-angiogenic agent to double-agent chemotherapy [15,16].

Vascular endothelial growth factor (VEGF) is a key molecular target in the treatment of NSCLC [17,18], and the combination of VEGF-directed anti-angiogenic therapy with platinum-based doublet chemotherapy offers potential for improved outcomes in advanced NSCLC [15,19,20]. Bevacizumab, a recombinant humanised anti-VEGF monoclonal antibody with a plasma half-life of approximately 3 weeks [21], was the first anti-angiogenic agent to show a survival benefit when combined with standard cytotoxic chemotherapy in advanced non-squamous NSCLC, extending median overall survival beyond 12 months [22]. However, the use of bevacizumab is restricted by the risk of high-grade bleeding [23], including potentially fatal pulmonary haemorrhage [24], particularly among patients with squamous NSCLC [25]. Phase II evidence implicating squamous histology as a risk factor for bevacizumab-induced pulmonary haemorrhage [26] resulted in exclusion of patients with squamous NSCLC from subsequent clinical trials.

Axitinib (Inlyta®; Pfizer Inc, New York, NY, USA) is an orally active and potent small-molecule tyrosine kinase inhibitor that produces broad inhibition of the VEGF pathway by targeting all three VEGF receptor subtypes (VEGFR1, VEGFR2 and VEGFR3) and has a short plasma half-life of 2 to 5 hours [27]. Axitinib shows evidence of single-agent activity in advanced NSCLC [28], and acceptable toxicity, both as monotherapy [28,29] and as chemotherapy, when in combination with cisplatin plus gemcitabine or carboplatin plus paclitaxel [30].
The objective of this phase II study was to assess the safety and efficacy of axitinib in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced/metastatic squamous NSCLC, who are considered to be at elevated risk of fatal pulmonary haemorrhage from bevacizumab-containing regimens.

PATIENTS AND METHODS

Patient selection

Patients aged \( \geq 18 \) years with histologically or cytologically confirmed squamous NSCLC that was locally advanced (stage IIIB) with pleural effusion or metastatic (stage IV) or recurrent, and with measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST) [31] were eligible for study inclusion. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate renal and hepatic function and adequate bone marrow reserve (absolute neutrophil count \( \geq 1,500 \) cells/\( \mu \)L, platelets \( \geq 100,000 \) cells/\( \mu \)L).

Patients were excluded from the study if they had received prior systemic therapy for stage IIIB/IV NSCLC (prior surgery or radiotherapy was permitted if completed \( \geq 4 \) and \( \geq 3 \) weeks, respectively, before enrolment) or prior anti-VEGF therapy; had lung lesions with cavitation or major blood vessel involvement, uncontrolled brain metastases or seizures, active malignancies other than NSCLC, gastrointestinal abnormalities or uncontrolled hypertension (systemic blood pressure [BP] \( > 140/90 \) mm Hg); had experienced cardiovascular/cerebrovascular disease, bleeding diathesis or coagulopathy within 12 months of study entry or
epileptic seizures or grade ≥3 haemoptysis/haemorrhage within 4 weeks of study entry; or had current or anticipated use of anti-coagulants or drugs known to be potent cytochrome P450 (CYP) 3A4 inhibitors or CYP1A2 or CYP3A4 inducers.

**Study design and treatment**

This open-label, single-arm study was conducted at 10 centres in Poland, Romania, Ukraine and South Africa, from 17 December 2008 to 30 November 2011. The primary study endpoint was objective response rate, as defined by RECIST criteria; secondary endpoints included progression-free survival, overall survival, duration of response and safety. Progression-free survival was defined as the time from commencement of study medication to documentation of disease progression or death, whichever occurred first. Overall survival was defined as the time from commencement of study medication to death from any cause. Duration of response was defined as the time from first documentation of response to documentation of disease progression or death, whichever occurred first.

The study was approved by the independent ethics committee at each participating centre and was conducted in accordance with the Declaration of Helsinki and relevant International Conference on Harmonisation Good Clinical Practice guidelines. Written informed consent was obtained from all patients before entry into the study. The study is listed in the US National Institutes of Health ClinicalTrials.gov registry under the identifier NCT00735904 [32].
All patients received standard platinum-based doublet chemotherapy (cisplatin/gemcitabine) plus axitinib. Cisplatin (80 mg/m\(^2\) intravenous infusion) was administered on day 1 and gemcitabine (1,250 mg/m\(^2\) intravenous infusion) on days 1 and 8 of each 21-day cycle of chemotherapy, for a maximum of six cycles. Axitinib was administered orally on a continuous schedule at a starting dose of 5 mg twice daily (bid) and was continued as maintenance therapy after completion of chemotherapy until disease progression. The starting dose for axitinib (5 mg bid) was selected based on a phase I study of axitinib in combination with cisplatin/gemcitabine that indicated that a starting dose of 5-mg bid axitinib could be safely combined with standard doses of cisplatin/gemcitabine [30]. Axitinib could be up-titrated incrementally to 7 mg bid and then to a maximum dose of 10 mg bid if the patient showed no treatment-related grade \(\geq 3\) toxicity during 2 weeks of treatment with the existing dose. Dose up-titration was not permitted if the patient had a BP >150/90 mm Hg or was receiving anti-hypertensive therapy. Chemotherapy dose reductions were based on the maximum grade of haematological and non-haematological toxicities observed during the previous treatment cycle and on the day of initiation of the current dose. Subsequent chemotherapy dose re-escalation was permitted at the investigator’s discretion in the absence of grade \(\geq 3\) haematological and grade \(\geq 2\) non-haematological toxicities during the previous treatment cycle. Patients who discontinued chemotherapy due to toxicity were allowed to continue with axitinib monotherapy.
Stepwise reductions in axitinib dose from a starting dose of 5-mg bid to a minimum of 2-mg bid were mandated by the occurrence of treatment-related toxicities of grade ≥3 severity. In the event of marked hypertension (BP >160/105 mmHg), haemoptysis, proteinuria or grade 4 toxicity, axitinib treatment was interrupted until its resolution and restarted at a lower dose. Axitinib treatment was permanently discontinued if patients required axitinib dose reduction below 2-mg bid or dose interruption for >4 weeks, or if they showed evidence of nephrotic syndrome, lung cavitation or delayed (>1 week) resolution of haemoptysis. Patients who discontinued axitinib due to toxicity were allowed to continue with scheduled chemotherapy. Concomitant administration of potent CYP3A4/5 inhibitors and inducers, CYP1A2 and CYP2C8 substrates, non-steroidal anti-inflammatory drugs and coumarin-derivative anti-coagulants was discouraged during the study.

Study assessments

Tumour response was assessed by computed tomography (CT) or magnetic resonance imaging at baseline (within 28 days before commencing study treatment) and was repeated every 6 weeks during chemotherapy and every 8 weeks during axitinib maintenance therapy, using RECIST criteria. Complete and partial tumour responses were confirmed 4 weeks after first documentation. Physical examinations and serum chemistry and urinalysis tests were performed at baseline, and were repeated at 3- and 4-week intervals during chemotherapy and axitinib maintenance therapy, respectively. Haematology tests were
performed at baseline, on days 1 and 8 of each cycle of chemotherapy and at 4-week intervals during axitinib maintenance therapy. Patients self-monitored their blood pressure bid during the study. Patients were followed-up at 2-month intervals after the final study visit to determine survival status. Patients who were not known to be deceased at the time of database closure were censored on the day when they were last known to be alive. Adverse events (AEs) were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [33].

Statistical analyses
The study sample size (an accrual target of 36 patients) was based on a single-stage design to test the null hypothesis that the true objective response rate to treatment was ≤40% versus the alternative hypothesis that the true objective response rate was ≥60%, with type I and II error levels of 0.10 and 0.15, respectively. Efficacy and safety analyses were conducted on the intent-to-treat (ITT) population, which comprised all patients who received at least one dose of study medication. Descriptive statistics were used to summarise continuous variables, and frequency and percentages to summarise categorical variables. Two-sided 95% confidence intervals (CI) for objective response rates were calculated using the exact method based on the F distribution. Time-to-event endpoints (overall survival, progression-free survival and duration of response) were estimated using Kaplan-Meier survival analysis. The median time-to-event and 95% CI were determined for each endpoint.
RESULTS

Patient characteristics and treatment

A total of 38 chemotherapy-naïve patients with advanced or metastatic squamous NSCLC were included in the study and received at least one dose of study medication (ITT population). Patients' baseline demographics and clinical characteristics are summarised in Table 1. The majority of patients were white (97.4%), male (89.5%), had a history of smoking (86.8%) and had stage IV disease (86.8%). Eighteen (47%) patients received the maximum six cycles of combined gemcitabine/cisplatin chemotherapy. The median number of chemotherapy cycles started was 4 (range, 1–6). The median duration of axitinib therapy was 3.1 (range, 0.2–22) months, and 17 (44.7%) patients went on to receive axitinib maintenance therapy after chemotherapy. The median dose of axitinib administered during the study was 10.0 mg/day (range, 6.2–19.6 mg/day).

The majority (92.1%) of patients received concomitant medication during the study, most commonly ondansetron, dexamethasone or furosemide.

Efficacy

The investigator-assessed objective response rate (complete and partial responses) for the ITT population (n = 38) was 39.5% (95% CI, 24.0–56.6%). One (2.6%) patient had a confirmed complete response and 14 (36.8%) patients had a confirmed partial response on study medication; stable disease was reported in nine (23.7%) patients and disease progression in three (7.9%)
patients (Table 2). Eight patients were ineligible for assessment of tumour response since the scheduled post-baseline CT scan was either unavailable or performed >28 days after the last study dose. Two further patients died before their first scheduled on-study tumour assessment (week 6 of chemotherapy) and one patient (excluded for protocol violation) did not undergo baseline tumour assessment. The median duration of response for patients with an objective tumour response (n = 15) was 5.8 months (95% CI, 4.7–7.2 months).

Median progression-free survival after commencement of study medication was 6.2 months (95% CI, 4.5–9.3 months) (Figure 1). Median overall survival was 14.2 months (95% CI, 11.8–23.1 months) (Figure 2). The probabilities of 12-month and 24-month survival were 63.2% (95% CI, 44.7–76.9%) and 30.8% (95% CI, 15.5–47.7%), respectively. In total, 21 (55.3%) patients died during the study (four patients during the study treatment period and 17 patients during follow-up).

Safety

A total of 36 (94.7%) patients reported at least one AE (all-causality) of any grade, of which the most frequent were nausea (42.1%), anaemia (31.6%), vomiting (28.9%), hypertension (26.3%), neutropaenia (23.7%), weight loss (23.7%) and decreased appetite (21.1%) (Table 3). The most commonly reported grade ≥3 AEs were neutropaenia (13.2%), hypertension (13.2%), anaemia (7.9%) and fatigue (7.9%) (Table 3). Overall, 34 (89.5%) patients experienced treatment-related AEs (all grades). Fifteen (39.5%) patients experienced serious
AEs while on treatment, with anaemia, pneumonia, dehydration and disease progression (n = 2 each [5.3%]) most frequent.

Fatal pulmonary haemorrhage is one of the major safety concerns in patients receiving anti-angiogenic therapy for squamous NSCLC. Three (7.9%) patients had haemoptysis, including two patients with grade 1 severity and one patient with grade 5 severity. The latter patient developed massive haemoptysis on day 16 of the first treatment cycle and died later that day from NSCLC; there was no prior evidence of tumour cavitation on CT scan or X-ray, and no obvious risk of haemoptysis in the patient’s medical history. One case of grade 1 haemoptysis was considered to be related to axitinib treatment. Three (7.9%) patients had elevated systolic BP (≥160 mm Hg) during the study, whereas none had elevated diastolic BP (≥105 mm Hg). Clinically significant laboratory abnormalities included elevated alanine aminotransferase (5.3%) and aspartate aminotransferase (2.6%), increased blood creatinine (5.3%) and reduced renal creatinine clearance (13.2%).

Treatment-emergent AEs resulted in at least one dose interruption in 13 (34.2%) patients, and dose reduction in five (13.2%) patients. The most frequent reasons for dose interruption were vomiting and anaemia (n = 3 each [7.9%]) and nausea, fatigue, dyspnoea and hypertension (n = 2 each [5.3%]), whereas the most frequent reason for dose reduction was hypertension (n = 2 [5.3%]). Overall, eight (21.1%) patients discontinued treatment due to AEs during the study, with four (10.5%) patients discontinuing because of drug-related toxicity (reduced renal creatinine clearance, pulmonary cavitation, pulmonary embolism and
hypertension, \( n = 1 \) each). Four (10.5%) patients died while on treatment (disease progression, \( n = 3 \); cerebrovascular accident and multiple organ failure, \( n = 1 \)).

**DISCUSSION**

This single-arm phase II study demonstrated that the combination of axitinib with cisplatin/gemcitabine has anti-tumour activity in advanced/metastatic squamous NSCLC, as reflected in an objective response rate of 39.5% (95% CI, 24.0–56.6%), a median overall survival of 14.2 months (95% CI, 11.8–23.1 months) and a 1-year survival rate of 63.2% (95% CI, 44.7–76.9%). The confirmed objective response rate (based on investigator assessment) was, however, only marginally higher than that previously reported with doublet chemotherapy (17% to 38%) in advanced NSCLC [4-11] and, accordingly, the null hypothesis that the true response rate is \( \leq 40\% \) was not rejected. The median overall survival of 14.2 months with the combination of axitinib plus cisplatin/gemcitabine was appreciably higher than most previously reported results for the doublet chemotherapy in NSCLC, where median overall survival ranged between 7.0 and 12.9 months [6-10,34] and was similar to a previous study where the median overall survival was 14.0 months with the doublet chemotherapy [8]. The 1-year survival rate of 63.2% appear to be only marginally higher than the 55.9% [6] and 59.6% [8] reported previously for cisplatin/gemcitabine treatment.
The toxicities caused by the combination of axitinib with standard chemotherapy were manageable in this selected patient population. The pattern and frequency of AEs observed during the study — predominantly nausea, anaemia, vomiting, hypertension, neutropaenia, weight loss, decreased appetite and fatigue — were consistent with the oncology setting and reflect the overall poor health of patients with advanced/metastatic NSCLC. Of note, life-threatening pulmonary haemorrhage, which is a particular safety concern with anti-angiogenic agents in squamous NSCLC [25], was detected in one (2.6%) patient who experienced fatal grade 5 haemoptysis during the first treatment cycle. No risk factors for haemoptysis were identified in the patient’s medical history. In contrast, a randomised phase II study of bevacizumab, carboplatin and paclitaxel combination therapy in advanced NSCLC reported four cases of life-threatening pulmonary haemorrhage among 13 (30.8%) patients with squamous histology [26]. The long plasma half-life of bevacizumab may have contributed to the severity of pulmonary haemorrhage, since its anti-angiogenic effect cannot be reversed rapidly.

Single-agent tyrosine kinase inhibitors, including axitinib, have proved to be generally well tolerated in patients with NSCLC [28,35-38]. The most common treatment-related AEs reported with axitinib monotherapy in NSCLC include fatigue, anorexia, diarrhoea and nausea, and these can be managed with dose modification and/or supportive treatment [28]. Although hypothyroidism has been linked with fatigue as a class effect of VEGFR-targeted therapy [39], we found no evidence of an increase in thyroid-stimulating hormone levels during the study.
Hypertension, which is commonly observed with anti-angiogenic agents [40], occurred in one in four axitinib-treated patients, but was managed through use of anti-hypertensive treatment or axitinib dose reduction. Due to their ability to inhibit multiple angiogenesis pathways, tyrosine kinase inhibitors offer the potential for improved efficacy and decreased secondary resistance [41]. In this study, the combination of axitinib with cisplatin/gemcitabine provided similar response rate and median overall survival when compared with corresponding historical data for cisplatin/gemcitabine chemotherapy alone. These results are consistent with previously reported studies of combined chemotherapy with axitinib [42] and other angiogenic tyrosine kinase inhibitors in NSCLC [43-45]. A recent randomised phase II trial of axitinib in combination with pemetrexed/cisplatin in patients with non-squamous NSCLC showed that the addition of axitinib resulted in numerically higher objective response rate but did not significantly improve median progression-free survival or median overall survival compared with chemotherapy alone [42]. The Motesanib NSCLC Efficacy and Tolerability (MONET1) study, which assessed the effect of adding motesanib, a small-molecule targeted antagonist of VEGFR-1, 2 and 3, to doublet chemotherapy (carboplatin and paclitaxel) compared with chemotherapy alone for first-line therapy of non-squamous NSCLC, reported a significant improvement in tumour response rate (40% vs. 26%, respectively), but no benefit in overall survival (median 13 vs. 11 months, respectively) [45]. Likewise, two randomised phase III trials, Evaluation of Sorafenib, Carboplatin and Paclitaxel Efficacy (ESCAPE) and NSCLC Research Experience Using
Sorafenib (NEXUS), found no significant survival benefit from addition of sorafenib to platinum-based chemotherapy in unresectable stage IIIb/IV NSCLC [43,44]. Indeed, in patients with squamous histology, sorafenib appeared to reduce median overall survival (8.9 vs. 13.7 months, sorafenib plus chemotherapy vs. chemotherapy alone, respectively); however, it should be noted that the overall survival time of patients receiving chemotherapy alone in the ESCAPE trial (median 13.7 months) was much greater than expected [44]. Taken together, these results may suggest that the combination of chemotherapy plus multi-targeted anti-angiogenic tyrosine kinase inhibitor therapy may not be advantageous over chemotherapy alone in terms of overall response rate, progression-free survival and overall survival in advanced NSCLC.

The results of this study should be considered with respect to its limitations. This was a single-arm study with a small number of patients. With the lack of a reference arm (cisplatin/gemcitabine alone), the results were compared with previous studies and these historical cross-trial comparisons should be interpreted with caution because of potential differences in each study, including the inclusion/exclusion criteria, diagnosis and staging and other differences [46].

CONCLUSIONS

In conclusion, the combination of axitinib with cisplatin plus gemcitabine demonstrated anti-tumour activity in patients with advanced/metastatic squamous NSCLC. Further, the safety profile was consistent with the oncology setting and reflects the overall poor health of these patients. Severe pulmonary
haemorrhage, a potential life-threatening toxicity associated with anti-angiogenic
treatment of squamous NSCLC, occurred in one patient. The study findings
provide preliminary indications that median overall survival in advanced NSCLC
can be extended beyond the 12-month threshold. However, due to the absence
of a reference arm of cisplatin/gemcitabine alone in this study, it is not conclusive
whether the combined treatment is better than chemotherapy alone. Further
investigation of this drug combination in a randomised controlled trial is
warranted.

LIST OF ABBREVIATIONS

AE, adverse event; bid, twice daily; BP, blood pressure; CI, confidence interval;
CT, computed tomography; CYP, cytochrome P450; ECOG, Eastern Cooperative
Oncology Group; ITT, intent to treat; NSCLC, non–small-cell lung cancer;
RECIST, Response Evaluation Criteria in Solid Tumours; SD, standard deviation;
VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth
factor receptor

COMPETING INTERESTS

AI and PB are employees of Pfizer Inc and own stock in Pfizer. SK was employed
at Pfizer Inc at the time of the study and in development of this manuscript, is
currently employed by Mirna Therapeutics and owns stock in Pfizer and Mirna. IB
and CC declare no conflicts of interest.
AUTHOR CONTRIBUTIONS
AI, PB and SK participated in the design and implementation of the study. IB and CC were principal investigators. All authors contributed to the interpretation of the data and to the development of the manuscript and approved the final manuscript.

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Table 1 Baseline demographics and clinical characteristics of the ITT population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cisplatin + gemcitabine + axitinib (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>60.5 (7.1)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>59.5 (47–73)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (89.5)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>37 (97.4)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>33 (86.8)</td>
</tr>
<tr>
<td>Tumour response, n (%)</td>
<td>Cisplatin + gemcitabine + axitinib (n = 38)</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Partial response</td>
<td>14 (36.8)</td>
</tr>
</tbody>
</table>

Non-smoker 5 (13.2)

Tumour histology

- Squamous cell carcinoma 38 (100)

Disease stage

- IIIB 5 (13.2)
- IV 33 (86.8)

ECOG performance status

- 0 12 (31.6)
- 1 26 (68.4)

Prior surgery

- Bronchoscopy 11 (28.9)
- Lymph node/pleural biopsy 6 (15.8)
- Lobectomy 2 (5.2)
- Thoracic wall resection 1 (2.6)

Values are n (%) unless otherwise noted. ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; SD, standard deviation.

Table 2 Summary of tumour responses during the study period for the ITT population*

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602 Values are n (%) unless otherwise noted. ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; SD, standard deviation.

604

605 Table 2 Summary of tumour responses during the study period for the ITT population*

606
<table>
<thead>
<tr>
<th>Response Type</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable disease</td>
<td>9 (23.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Indeterminate response†</td>
<td>8 (21.1)</td>
</tr>
<tr>
<td>Not assessed due to early death‡</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Baseline status uncertain§</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td><strong>Objective response (complete + partial)</strong></td>
<td><strong>15 (39.5)</strong></td>
</tr>
</tbody>
</table>

**Table 3 Summary of all-causality adverse events occurring in >2 patients in the ITT population during the study period**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All grades</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>42.1</td>
</tr>
<tr>
<td>Anaemia</td>
<td>12</td>
<td>31.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>28.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
<td>26.3</td>
</tr>
</tbody>
</table>

ITT = intent-to-treat.  
*Study period comprised the treatment period plus 28-day follow-up period after the last dose of study drug.  
†Imaging scans unavailable or performed >28 days after the last study dose.  
‡Death occurring before the first scheduled tumour assessment.  
§No baseline assessment performed.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Availabilty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropaenia</td>
<td>9</td>
<td>23.7</td>
<td>5</td>
<td>13.2</td>
</tr>
<tr>
<td>Weight loss</td>
<td>9</td>
<td>23.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>8</td>
<td>21.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7</td>
<td>18.4</td>
<td>3</td>
<td>7.9</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6</td>
<td>15.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leukopaenia</td>
<td>5</td>
<td>13.2</td>
<td>2</td>
<td>5.3</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5</td>
<td>13.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reduced creatinine clearance</td>
<td>5</td>
<td>13.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5</td>
<td>13.2</td>
<td>0</td>
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<td>Rash</td>
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</table>

ITT = intent-to-treat.

*Study period comprised the treatment period plus 28-day follow-up period after the last dose of study drug.

Figure Legends
Figure 1 Kaplan-Meier curve of progression-free survival for the ITT population (n = 38). ITT, intent-to-treat

Figure 2 Kaplan-Meier curve of overall survival for the ITT population (n = 38). ITT, intent-to-treat

Figures

Figure 1

Figure 2
Number of patients at risk

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</thead>
<tbody>
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</tbody>
</table>

Overall survival probability
Figure 2: Overall survival probability over time (months) for patients at risk.
Additional files provided with this submission:

Additional file 1: Cover Letter.docx, 19K
http://www.biomedcentral.com/imedia/1481662299142135/supp1.docx
Additional file 2: Potential reviewers.docx, 15K
http://www.biomedcentral.com/imedia/7406158221421352/supp2.docx