厚生労働科学研究費補助金
がん対策推進総合研究事業
（革新的がん医療実用化研究事業）

進行非小細胞肺癌を対象としたエルロチニブとYM155の分子標的治療薬併用第I相試験

平成２６年度　総括研究報告書

研究代表者　中川　和彦

平成２７（２０１５）年　３月

別添１

厚生労働科学研究費補助金研究報告書表紙

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別添５

研究成果の刊行に関する一覧表

別紙１

厚生労働科学研究費補助金

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進行非小細胞肺癌を対象としたエルロチニブとYM155の分子標的治療薬併用第I相試験

研究代表者　中川　和彦
近畿大学医学部内科学腫瘍内科部門　教授

研究要旨　進行非小細胞肺癌患者を対象に、EGFRチロシンキナーゼ阻害剤(EGFR-TKI)エルロチニブに併用するサバイビン阻害薬YM155の推奨投与量の設定、及び用量制限毒性（DLT）を明らかにし、推奨投与量における安全性と抗腫瘍効果および効果に関わるバイオマーカーを探索する

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西尾　和人　（近畿大学医学部ゲノム生物学教室　教授）
坂井　和子　（近畿大学医学部ゲノム生物学教室　助教）
千葉　康敬　（近畿大学医学部附属病院臨床研究センター　講師）

A．研究目的

EGFR陽性進行非小細胞肺癌患者を対象に、EGFRチロシンキナーゼ阻害剤(EGFR-TKI)エルロチニブに併用するサバイビン阻害薬YM155の推奨投与量の設定、及び用量制限毒性（DLT）を明らかにし、推奨投与量における安全性と抗腫瘍効果および効果に関わるバイオマーカーを探索する。

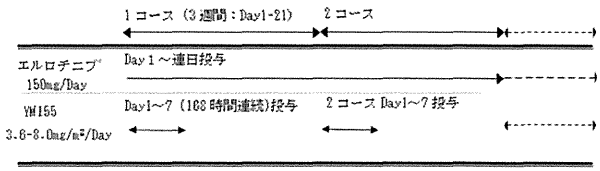
B．研究方法

[研究計画・方法]
分子標的治療薬併用第Ｉ相臨床試験（医師主導治験）として、進行非小細胞肺癌に対する化学療法を受ける患者を対象にエルロチニブとYM155併用投与の両薬剤推奨投与量の設定、用量制限毒性（DLT）および最大耐用量（MTD）を明らかにし、両分子標的治療薬の推奨投与量における安全性と抗腫瘍効果について検討する。

[対象症例]
進行非小細胞肺癌に対する化学療法を受ける患者、20歳以上、ECOG Performance Status (PS) 0-2、主要臓器機能が保持された症例。患者本人の自由意思による文書同意を必須とする。

【Primary endpoint】
エルロチニブとYM155併用投与の安全性プロファイル（有害事象）、用量制限毒性（DLT : dose limiting toxicity）、最大耐用量（MTD : maximum tolerated dose）および推奨投与量の決定。

【Secondary endpoint】
推奨投与量における安全性と抗腫瘍効果、及び抗腫瘍効果に関わるバイオマーカーの探索。



エルロチニブは１日１錠(150mg)の連日投与とし、YM155（アステラス製薬より供給予定）は（シリンジポンプを用いた）168時間（7日間）の持続点滴静脈内投与とする。併用治療開始時点を1コースday１とする。エルロチニブは連日投与、YM155は1週間(168時間)投与2週間休薬をもって1コース（21日間隔）とする。以後、腫瘍の増悪、新病変の出現または投与継続が困難な有害事象の発現を認めるまで、1コースを21日間隔として治療を継続する。パート1(dose escalation cohort)の症例では、プロトコール本文に記載のスケジュールにてエルロチニブ及びYM155の薬物動態測定（血漿及び尿検体）を行う。また同意が得られた患者に対し、抗腫瘍効果に関わるバイオマーカーの探索として1)YM155投与前後における腫瘍組織中のサバイビン蛋白質量の測定とアポトーシス誘導の有無を確認、2)肺癌組織の体細胞変異解析にあたり、LungCarta、Bio-plex (Ligand panel)等のマススクリーニングパネルを用いた半網羅的体細胞変異解析を行う。

[予定症例数及び研究期間]
医師主導治験による第Ｉ相臨床試験として、12-24例。試験期間は2012年12月1日より2015年11月31日（準備期間：1年、登録期間: 1年、追跡期間：1年）とする。

[研究体制]
研究代表者（医師主導治験実施責任者）は研究の統括・計画を実施する。研究分担者は近畿大学医学部腫瘍内科において研究の計画・測定・解析を実施、症例登録を行う。バイオマーカーの測定は近畿大学医学部ゲノム生物学教室で測定する。近畿大学医学部・医学部附属病院および外部CROであるクインタ

イルズ・ジャパン・データマネジメント部および日本臨床研究オペレーションズ（Japan Clinical Research Operations:JCRO)は近畿大学医学部腫瘍内科と共同して本医師主導治験運用に必須であるセンターデータマネージメント、モニタリング業務、治験薬管理（治験薬剤提供元企業との連携）、CRC業務およびローカルデータマネージメント業務を遂行する。統計解析は近畿大学医学部臨床研究センター腫瘍統計学部門および外部CROであるクインタイルズ・ジャパン・データマネジメント部が行う。研究実施環境については研究施設・研究資料・研究フィールド・現在の研究環境の状況等インフラ整備されており問題はない。

（倫理面への配慮）
試験に関係するすべての研究者は、ヘルシンキ宣言および臨床研究に関する倫理指針にしたがって本試験を実施し，以下の事項を厳守する.
1. 登録に先立って、すべてに患者に施設の倫理審査委員会（IRB）承認が得られた説明文書を用いて十分な説明を行い，考慮の時間を設けた後に患者自身の自由意志による同意を文書にて取得るする。
2. 個人情報および診療情報などのプライバシーに関する情報は個人の人格尊重の理念の下、厳重に保護され慎重に取り扱われるべきものと認識し、万全な管理対策を講じ、プライバシー保護に努める。データの取り扱いに関しては直接個人を識別できる情報を用いず，データベースのセキュリティーを確保し，個人情報の保護を厳守する。
本研究に組み込まれるバイオマーカー研究は蛋白発現、体細胞DNAを対象に解析するものであり、「ヒトゲノム・遺伝子解析研究に関する倫理指針」の対象ではないが、その趣旨を踏まえた対応を行う。

C．研究結果
EGFR陽性進行非小細胞肺癌患者を対象に、分子標的治療薬併用第Ⅰ相臨床試験としてEGFR阻害薬エルロチニブ併用時における新規サバイビン阻害薬YM155の推奨投与量の設定、用量制限毒性（DLT）および最大 耐用量（MTD）を明らかにし、両分子標的治療薬の推奨投与量における安全性と抗腫瘍効果の検討及び抗腫瘍効果に関わるバイオマーカー探索を実施した。現況として当初の治験実施計画規定に基づく第１コホートレベル～第4コホートレベル迄の合計4段階用量漸増計画のうち、同事業完了時点において現在引き続き当施設に於いて残る最終の第4コホートレベル（合計3～6名予定）の被験者に対して治験薬を投与中であり、同医師主導治験完遂まで実施予定である。併用第Ⅰ相臨床試験の第3コホートレベル終了時までにおける研究結果として、
①安全性に関する評価に関しては第1コホートレベルから第3コホートレベル（合計12例）においては用量制限毒性（DLT）発現は全12症例中1症例のみに認められ（血清クレアチニン値上昇 2.4mg/dl NCI-CTC グレード2）、治験薬休薬中止にて可逆的に完全回復した。治療との因果関係が否定出来ない毒性に関してNCI CTC-AEグレード3以上の毒性に関してはYM155 第2コホートレベルにおいて1例のみ（下痢：グレード3）を認めたのみであり、最も高頻度の毒性に関しては皮疹（グレード2：45.5%、グレード1：45.5%）、疲労（グレード1：23.9%）、下痢（グレード3：9.1%、グレード2：9.1%、グレード1：18.2%）、尿中β2-ミクログロブリン上昇（グレード1：23.9%）、尿中NAG上昇（グレード1：23.9%）、血清クレアチニン上昇（グレード2：9.1%、グレード1：9.1%）、ヘモグロビン低下（グレード2：9.1%、グレード1：9.1%）、蛋白尿（グレード1：18.2%）、発熱（グレード1：9.1%）、低Na血症（グレード1：9.1%）、味覚異常（グレード1：9.1%）であり、全般的に忍容性は良好であった。
②有効性に関する評価に関しては全12症例中2症例において（それぞれYM155 第1コホートレベルおよび第3コホートレベル）6か月間以上の画像上の病勢安定（RECIST判定基準においてSD：Stable disease）および腫瘍縮小効果が認められた。
③抗腫瘍効果に関わるバイオマーカー探索研究として、治験薬投与前後（YM155投与前および2サイクル目投与期間中）の腫瘍組織採取（気管支鏡下肺生検もしくは転移病巣からの経皮的腫瘍針生検等）が採取施行可能例には被験者の同意取得のもとに実施されており、抗腫瘍効果に関わるバイオマーカーの探索として1)YM155投与前後における腫瘍組織中のサバイビン蛋白質量の測定（Survivin IHC、Survivin RT-PCR）とアポトーシス誘導の有無を確認、2)肺癌組織の体細胞変異解析にあたり、LungCarta Panel、Ion Ampliseq Panel （NGS：次世代シーケンサー）、Luminex Panel（血漿タンパク質解析）等のマススクリーニングパネルを用いた半網羅的体細胞変異解析を施行した。腫瘍組織中のサバイビン蛋白発現に関しては免疫組織染色（Survivin IHC）においてYM155投与前後において有意にサバイビン蛋白発現が低下する傾向を認めた。血液検体を用いたLuminex Panel（血漿タンパク質解析）においては抗腫瘍効果判定においてNon-PD（Progressive disease）群はPD群と比較してDay7以降のIL-1Ra, IL-2, IL-7,IL-12, IL-13, G-CSF, TNF-αが高値を示す傾向が認められた。効果予測因子となりうる血清バイオマーカーに関してEGFR阻害薬エルロチニブに関しては治療前のHGFおよびVEGF-A高値が、併用薬YM155に関しては治療前のIL-10, IL-12およびVEGF-A高値が予後不良と相関性傾向を示した。

同医師主導治験実施期間中に治験薬供給元であるアステラス製薬株式会社において他の開発品との優先度等を総合的に勘案し製薬企業側の戦略的観点から、治験薬YM155の今後の開発中止が決定された旨をアステラス製薬株式会社より報告を受けた。既に現在までに合計3回の外部委員による効果安全性委員会開催が施行されており、また治験薬に関する安全性・有効性以外の製薬企業理由による薬剤開発中止を受けた後における医師主導治験実施継続に関する妥当性に関してPMDA審査マネジメント部・アステラス製薬株式会社より問題はないものとの回答を得ており、平成27年4月20日当施設倫理委員会にての審議承認を経て、治験実施計画書に準じて予定通り最終コホートレベルである第4コホートレベルにおいて現在も医師主導試験実施中である。治験薬の安定性試験（延長申請済み：アステラス製薬品質保証部より再試験期限変更済み）結果に基づいた予定治験薬使用期限である平成27年9月末までに最終コホートレベルである第4コホートレベルを終了完結すべく現在も同内容に関して被験者へ十分なインフォームドコンセントを行ったうえで（同意説明文書改訂済・施設倫理委員会承認済）医師主導治験を実施中である。

D．考察

抗腫瘍効果に関わるバイオマーカー探索研究として、治験薬投与前後（YM155投与前および2サイクル目投与期間中）の腫瘍組織採取（気管支鏡下肺生検もしくは転移病巣からの経皮的腫瘍針生検等）が採取施行可能例には被験者の同意取得のもとに実施されており、抗腫瘍効果に関わるバイオマーカーの探索として1)YM155投与前後における腫瘍組織中のサバイビン蛋白質量の測定（Survivin IHC、Survivin RT-PCR）とアポトーシス誘導の有無を確認、2)肺癌組織の体細胞変異解析にあたり、LungCarta Panel、Ion Ampliseq Panel （NGS:次世代シーケンサー）、Luminex Panel（血漿タンパク質解析）等のマススクリーニングパネルを用いた半網羅的体細胞変異解析を施行した。腫瘍組織中のサバイビン蛋白発現に関しては免疫組織染色（Survivin IHC）においてYM155投与前後において有意にサバイビン蛋白発現が低下する傾向を認めた。血液検体を用いたLuminex Panel（血漿タンパク質解析）においては抗腫瘍効果判定においてNon-PD（Progressive disease）群はPD群と比較してDay7以降のIL-1Ra, IL-2, IL-7,IL-12, IL-13, G-CSF, TNF-αが高値を示す傾向が認められた。効果予測因子となりうる血清バイオマーカーに関してEGFR阻害薬エルロチニブに関しては治療前のHGFおよびVEGF-A高値が、併用薬YM155に関しては治療前のIL-10, IL-12およびVEGF-A高値が予後不良と相関性傾向を示した。臨床的に長いPFSを示した群においては抗アポトーシスケモカイン及びVEGFが低値を示し、抗アポトーシスが弱い腫瘍細胞においては、YM155によるアポトーシス易誘導可能性が示唆された。今後も適切な症例選択に基づくサバイビン阻害薬によるEGFR阻害薬耐性克服メカニズム可能性に関してバイオマーカーを含めた更なる探索が求められる。

E．研究発表

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G. 知的財産権の出願・登録状況

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　　なし

別紙５

研究成果の刊行に関する一覧表

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ORIGINAL ARTICLE

A phase 1 study of linifanib in combination with carboplatin/paclitaxel as first-line treatment of Japanese patients with advanced or metastatic non-small cell lung cancer (NSCLC)

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Abstract
Introduction Linifanib is a potent, orally active, and selective inhibitor of vascular endothelial growth factor and platelet-derived growth factor receptor kinase activities with clinical efficacy in non-small cell lung cancer (NSCLC). This phase 1 dose-escalation study evaluated the pharmacokinetics, safety, and efficacy of linifanib in combination with carboplatin/paclitaxel in Japanese patients with advanced NSCLC.
Methods Carboplatin (AUC = 6 mg/mL/min) and paclitaxel (200 mg/m^2) were administered on day 1 of each 21-day cycle up to a maximum of six cycles. Oral linifanib (7.5 mg) was given to six patients once daily throughout all cycles and escalated to 12.5 mg/day in a second cohort of six patients.
Results Twelve patients received at least one dose of linifanib. The most common adverse events were hematologic and consistent with expected toxicities with carboplatin/paclitaxel. With 12.5 mg linifanib, grade 3/4 neutropenia, leukopenia, and thrombocytopenia occurred in 100, 83, and 83 % of patients, respectively. Dose-limiting grade 4 thrombocytopenia occurred in one patient at each dose level. Linifanib pharmacokinetics was similar to that in non-Japanese patients. At 12.5 mg, linifanib C_{max} was 0.32 μg/mL and AUC_{24} was 4.29 μg h/mL. Linifanib C_{max} occurred at 2–3 h with both doses and when given alone or in combination with carboplatin/paclitaxel. Exposure to linifanib appeared to be increased by carboplatin/paclitaxel, and exposure to paclitaxel appeared to be increased by linifanib. Partial responses were observed in nine patients.
Conclusions Linifanib added to carboplatin/paclitaxel is well tolerated in Japanese patients with advanced/metastatic NSCLC. The recommended dose of linifanib with carboplatin/paclitaxel is 12.5 mg, same as for US patients.

Keywords Angiogenesis · Linifanib (ABT-869) · NSCLC · PDGFR · VEGFR

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Introduction

Treatment of advanced/metastatic non-small cell lung cancer (NSCLC) remains challenging. Compared with older regimens, platinum-based chemotherapy modestly extends survival of previously untreated patients with advanced NSCLC [1]. Further improvements in the treatment of advanced NSCLC are urgently needed. Molecular studies defining mutations involved in NSCLC have resulted in prolonged progression-free survival with agents targeting these mutations, but to the benefit of a small proportion of patients with NSCLC [2–5].

Growth of new blood vessels (angiogenesis), an important factor in the progression of most cancers, is regulated by growth factors, principally the vascular endothelial growth factors (VEGFs) and platelet-derived growth factors (PDGFs), and their production is prognostic in NSCLC.

For example, VEGF-A expression correlates with the development of metastatic disease and poor survival [6–9]. Bevacizumab, a monoclonal antibody to VEGF-A, added to standard carboplatin and paclitaxel chemotherapy for recurrent NSCLC increased progression-free survival (PFS) and extended overall survival (OS) for patients with advanced non-squamous NSCLC [10]. However, overall survival for the patients who received bevacizumab with their chemotherapy was only about 1 year.

PDGFs are also associated with a poor outcome in NSCLC and have the ability to contribute in several ways to angiogenesis and tumor progression [8]. Linifanib (ABT-869) is an orally active, selective tyrosine kinase inhibitor that targets VEGF and PDGF receptors with IC_{50} values in the low nanomolar range [11]. The breadth of its activity, potency, and selectivity against unrelated cellular kinases compares favorably with those of other small molecules targeting VEGF and PDGF receptors [12]. In preclinical studies, linifanib potentiated the activity of carboplatin and paclitaxel in a number of tumor models, including NSCLC [12, 13].

In previous clinical studies, linifanib demonstrated activity as a single agent in patients with advanced NSCLC, encouraging further evaluation of linifanib as a component of therapy for these patients [14–16]. In a phase 1 trial with 18 Japanese patients with advanced NSCLC and a median of 3 prior treatment regimens, the pharmacokinetics of oral once daily linifanib was reported as being dose proportional and unremarkable over the range of 0.10–0.25 mg/kg. The principal linifanib toxicities were hypertension, increased AST, rash, and neutropenia [16]. In a multinational (35 % Asian) study of 139 patients with relapsed NSCLC, randomized to receive linifanib 0.1 or 0.25 mg/kg, dose-related fatigue, loss of appetite, hypertension, diarrhea, nausea, palmar–plantar erythrodysesthesia (PPE), and proteinuria were seen in >20 % of patients, and grade 3 hypertension occurred in 14 % of patients [15, 16]. The pharmacokinetic profile was similar in Japanese, non-Japanese Asian, and Caucasian patients [16].

The combination of linifanib (7.5 or 12.5 mg flat dose) or placebo with carboplatin and paclitaxel was assessed for efficacy and safety in a randomized phase 2 study in 138 patients with advanced or metastatic, non-squamous NSCLC. Events occurring more frequently with treatment compared with the placebo arm included dose-related thrombocytopenia, hypertension, diarrhea, weight loss, and PPE. The only severe toxicity occurring more frequently in the treatment group was grade 3 thrombocytopenia in 17 % with 7.5 mg and 30 % with 12.5 mg linifanib. Responses were seen in 43, 32, and 26 % of patients with linifanib 7.5 mg, linifanib 12.5 mg, and placebo, respectively. PFS was extended from 5.4 to 8.3 months with the addition of linifanib 7.5 mg/day [17].

The objectives of this phase 1 trial were to evaluate the safety, tolerability, pharmacokinetics, and the recommended phase 2 dose of linifanib in combination with carboplatin and paclitaxel in Japanese patients with advanced/metastatic NSCLC.

Methods

Study design

This was an open-label, phase 1, dose-escalating, multicenter trial conducted at three sites in Japan (Registration NCT01225302). The study was approved by the Institutional Review Board at each study site and was conducted in accordance with the International Conference on Harmonization guidelines and the ethical principles of the Declaration of Helsinki. All patients provided written informed consent.

The doses tested in this phase 1 trial were selected on the basis of results of previous phase 1 and phase 2 studies in which linifanib doses of 7.5 and 12.5 mg/day showed no significant safety concerns. The primary study objective was to assess the safety and pharmacokinetics of linifanib and to identify the tolerable dose of linifanib in combination with carboplatin and paclitaxel in Japanese subjects with advanced or metastatic NSCLC. The secondary objective was to obtain a preliminary assessment of antitumor activity of the therapy as first-line treatment.

Patients

Patients were ≥20 years of age with cytologically or histologically confirmed advanced/metastatic (i.e., stage IIIb/IV) non-squamous NSCLC, measurable disease defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), an Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, no prior chemotherapy for NSCLC, and adequate bone marrow, renal, and hepatic function. Men and women of childbearing potential had to agree to use adequate contraception.

Patients were excluded if they had prior chemotherapy for NSCLC, radiation therapy, or surgery within 21 days prior to study drug, brain, or meningeal metastases that were symptomatic or required treatment, or radiologic evidence of tumor invading major blood vessels. Other exclusion criteria included current anticoagulation therapy, clinically significant bleeding ≤3 months, proteinuria, uncontrolled hypertension (i.e., >140/90 mm Hg), myocardial infarction or transient ischemic attack ≤6 months, left ventricular ejection fraction (LVEF) <50 %, autoimmune disease with renal involvement, or any medical condition that was clinically significant and uncontrolled or that may interfere with gastrointestinal absorption.

Treatment

All patients received standard carboplatin (AUC = 6 mg/mL/min) and paclitaxel (200 mg/m^2) on day 1 of each 21-day cycle. Patients received linifanib 7.5 mg/day beginning on day 3 of cycle 1. A second cohort received 12.5 mg/day after the first cohort of six patients demonstrated adequate tolerability [dose-limiting toxicity (DLT) in <3 of 6 patients]. Overall, 12 patients were enrolled, six at each linifanib dose level. Linifanib dose reduction (2.5 mg/reduction) or interruption was allowed for linifanib-related adverse events (AEs). Patients received up to a maximum of six cycles of carboplatin/paclitaxel and, after completing these cycles, could continue single-agent linifanib until disease progression or criteria for discontinuation were met. Carboplatin/paclitaxel dose reductions and delays followed procedures as defined in the locally approved product label.

Assessments

Study visits were conducted on day 1 weekly for the first two cycles (6 weeks) and then on day 1 of every subsequent 21-day cycle. A follow-up visit was performed 30 days after the last linifanib dose. Safety assessments included evaluation of AEs, laboratory profiles, physical examination, and vital signs throughout the study. During the first cycle (21 days), patients were hospitalized for the evaluation of DLT. AEs and DLT were defined according to CTCAE v4.0. DLT was defined as grade 4 neutropenia >7 days; grade 4 febrile neutropenia; grade 4 thrombocytopenia (<25,000/mm^3) or thrombocytopenia that requires transfusion due to persistent hemorrhage; grade ≥3 and uncontrollable hypertension; and grade ≥3 non-hematologic toxicity, with the exception of grade 3 febrile neutropenia, nausea, vomiting and anorexia, diarrhea, constipation, and electrolyte abnormality that were controlled with an intervention and that the investigator considered not to be a DLT. The investigator monitored patients for clinical and laboratory evidence of AEs routinely throughout the study. AEs were assessed for severity and relationship to study drug.

Blood samples for linifanib, carboplatin, and paclitaxel pharmacokinetic analyses were collected during cycles 1 and 2 of the study. Samples for the determination of carboplatin concentrations were obtained at hour 0 and at 0.92, 4, 5, and 21 h after the start of carboplatin infusion on day 1 of cycles 1 and 2. Samples for determination of paclitaxel concentrations were obtained at hour 0 and at 2.92, 4, 8, and 48 h after the start of paclitaxel infusion on day 1 of cycles 1 and 2. Samples for determination of linifanib concentration were collected on day 21 of cycle 1 and day 1 of cycle 2 at 0 h and at 2, 3, 4, 8, and 24 h after dosing. Plasma was stored at −20 °C until shipment to Abbott Laboratories (Abbott Park, IL). Standard pharmacokinetic parameters were determined using non-compartmental methods.

The effects of coadministration of paclitaxel/carboplatin on the pharmacokinetics of linifanib were evaluated by analyzing linifanib pharmacokinetic variables on cycle 2, day 1 (linifanib with carboplatin/paclitaxel) and cycle 1, day 21 (linifanib alone). Analysis of variance was performed including subject and day as classification variables. A point estimate and 90 % confidence interval (CI) were determined for the ratio of the central values for these dosing time points. Likewise, the effects of coadministration of linifanib on carboplatin and paclitaxel pharmacokinetics were assessed by measuring the pharmacokinetic parameters of carboplatin and paclitaxel on cycle 1, day 1 versus values on cycle 2, day 1 in a similar fashion.

Efficacy assessments included determination of tumor response and disease progression (PFS). Tumor response was evaluated by CT scan every 6 weeks using RECIST v1.1 criteria until progression.

Results

Patients and treatment

Twelve patients were enrolled (6 each receiving linifanib 7.5 or 12.5 mg) between September 2010 and June 2012, and all received at least one dose of study drug. Patient characteristics are summarized in Table 1. Dose interruptions/delays of linifanib or carboplatin/paclitaxel were observed in all patients. Reasons for patients discontinuing linifanib included progressive disease (n = 6), AEs (n = 5), and sponsor discontinuation of study (n = 1), and eight patients discontinued carboplatin/paclitaxel after 1–4 cycles (median 2.5 cycles) including 4 due to AEs. One or more reasons for study drug discontinuation were reported for each subject. The median number (and range) of treatment cycles with carboplatin/paclitaxel was 3 (1–6) and with linifanib was 4 (1–21+). The median exposure (and range) to linifanib was 66.0 days (16–449).

Safety

Linifanib in combination with carboplatin and paclitaxel was tolerated in this population of Japanese patients with advanced NSCLC. AEs were consistent with the known toxicities of the study medications. Overall, most linifanib-related AEs were mild to moderate in severity. All grade 3 and 4 AEs and those which occurred with at least grade 2 severity in two or more patients are shown in Table 2. The most common AEs were hematologic; neutropenia, leucopenia, thrombocytopenia, and anemia. The most common grade 3/4 AEs were neutropenia (92 %), leukopenia (67 %),

Table 1 Patient characteristics

Characteristic	All $N = 12$	Linifanib 7.5 mg $N = 6$	Linifanib 12.5 mg $N = 6$
Gender, male (%)	7	3	3
Age, mean (years)	60.4	64.0	56.8
Median (range)	61.5 (43–72)	64.5 (54–72)	56.0 (43–69)
ECOG PS (%)			
0	9	5	4
1	3	1	2
Tobacco use, *n* (%)			
Yes	9	4	5
Never	3	2	1
Adenocarcinoma, *n* (%)	12	6	6
Tumor stage, *n* (%)			
Stage IIIB	1	1	0
Stage IV	11	5	6
Prior oncology surgery	2	1	1
Prior radiation	2	1	1

ECOG PS Eastern Cooperative Oncology Group performance status

Table 2 Patients with linifanib-related adverse events

Adverse event	Linifanib 7.5 mg + C/P ($N = 6$)				Linifanib 12.5 mg + C/P ($N = 6$)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	1	2	2	1	0	1	4	1
Neutropenia	0	0	0	5	0	0	4	2
Anemia	2	2	1	0	3	1	2	0
Leukopenia	0	1	3	0	0	1	5	0
Alopecia	4	0	0	0	2	2	0	0
Skin eruption	3	1	0	0	3	1	0	0
Weight decreased	2	1	0	0	2	2	0	0
Hypertension	0	1	1	0	1	3	0	0
Anorexia	2	1	0	0	2	1	0	0
Diarrhea	2	2	0	0	1	1	0	0
Febrile neutropenia	0	0	2	0	0	0	2	0
PPE syndrome	1	1	0	0	1	1	0	0
Hyperglycemia	1	0	0	0	1	2	0	0
Lymphopenia	1	0	0	0	1	0	1	0
Hypophosphatemia	0	1	0	0	0	2	0	0
Stomatitis	1	1	0	0	0	1	0	0

Highest grade for each patient

C/P carboplatin/paclitaxel, *PPE* palmar–plantar erythrodysesthesia

and thrombocytopenia (67 %). One patient in each linifanib dose cohort developed a serious AE, grade 3 febrile neutropenia, and a DLT of grade 4 thrombocytopenia was experienced by two patients, one patient in each cohort. Five patients experienced a treatment-emergent AE that led to discontinuation of study drug, the most frequent being neutropenia (33 %). Other AEs commonly associated with antiangiogenic agents were seen: grade 2 fatigue and proteinuria in one patient each and grade 1 proteinuria in three patents. There were no clinically significant abnormalities in laboratory chemistries or urinalysis, and no clinically meaningful changes in cardiac function (LVEF). Changes in vital signs (fever, weight loss, hypertension) occurred in 11 patients, and these were low grade except for grade 3 hypertension in one patient. There were no treatment-related deaths.

Pharmacokinetics

Pharmacokinetic parameters are summarized in Table 3. Maximum plasma linifanib concentrations (C_{max}) were observed at approximately 2–3 h after administration. C_{max}

Table 3 Pharmacokinetic parameters of linifanib, carboplatin, and paclitaxel administered alone and in combination with Japanese patients

PK parameter	Monotherapy		Combination	
	7.5 mg	12.5 mg	7.5 mg	12.5 mg
Linifanib				
N	5	5	4	2
T_{max} (h)	2.4 ± 0.5	2.4 ± 0.5	3.3 ± 0.5	3.5 (3.0, 4.0)[b]
C_{max} (μg/mL)	0.25 ± 0.03	0.32 ± 0.05	0.33 ± 0.10	0.45 (0.46, 0.43)[b]
C_{max}/dose (μg/mL/mg)	0.033 ± 0.004	0.025 ± 0.004	0.043 ± 0.013	0.036 (0.037, 0.034)[b]
AUC_{24} (μg h/mL)	3.49 ± 0.72[a]	4.29 ± 0.48[a]	5.06 ± 1.11	6.56 (6.56, 6.56)[b]
AUC_{24}/dose (μg h/mL/mg)	0.465 ± 0.096[a]	0.344 ± 0.038[a]	0.675 ± 0.148	0.524 (0.524, 0.524)[b]
Carboplatin				
N	6	6	4	2
T_{max} (h)	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	0.9 (0.9, 0.9)[b]
C_{max} (μg/mL)	22.9 ± 2.7	23.0 ± 3.3	26.5 ± 6.1	28.6 (28.8, 28.3)[b]
AUC_{21} (μg h/mL)	96.8 ± 16.8	90.3 ± 8.5	105.5 ± 17.6	101.8 (107.0, 96.6)[b]
Paclitaxel				
N	6	6	4	2
T_{max} (h)	2.9 ± 0.0	2.9 ± 0.0	2.9 ± 0.0	2.9 (2.9, 2.9)[b]
C_{max} (μg/mL)	7.6 ± 1.8	6.5 ± 2.7	9.8 ± 1.3	8.3 (8.3, 8.3)[b]
AUC_{48} (μg h/mL)	34.7 ± 8.7	28.9 ± 13.0	48.1 ± 4.6	34.7 (35.6, 33.9)[b]

[a] $N = 4$

[b] Mean (individual values)

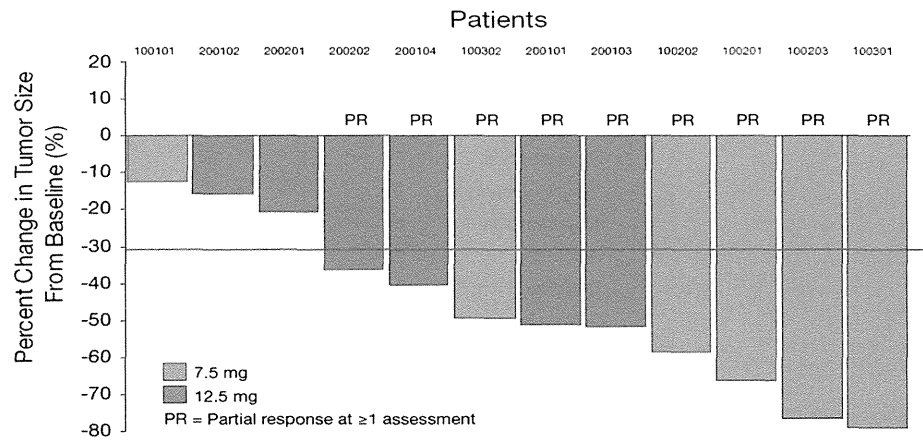

Fig. 1 Best percentage change (decrease) in tumor size from baseline. Nine patients achieved a partial response; of these, six were confirmed

and AUC from time zero to 24 h post-dose (AUC_{24}) of linifanib appeared to be increased by coadministration of carboplatin/paclitaxel. The ratios of central values of dose-normalized linifanib with and without coadministration of carboplatin/paclitaxel showed an increase of 36 % (90 % CI 12–66 %) in C_{max} and 55 % (90 % CI 22–97 %) in AUC_{0-24}.

Paclitaxel exposure appeared to be increased by coadministration of linifanib. The ratios of central values of dose-normalized paclitaxel C_{max} and AUC_{0-21} with and without coadministration of linifanib were increased by 59 % (90 % CI 32–90 %) in C_{max} and 62 % (90 % CI 41–87 %) in AUC_{0-21}. In contrast, the pharmacokinetics of carboplatin was not affected by coadministration of linifanib. Plasma exposure to linifanib was higher in 12.5 mg linifanib cohort compared to that in the 7.5 mg linifanib cohort. The exposures to carboplatin and paclitaxel were comparable between the two cohorts.

Efficacy

Antitumor activity was observed in all 12 patients (Fig. 1). There were nine partial responses (5 in 7.5-mg group and 4 in 12.5-mg group) and 3 with stable disease, for an overall response rate of 75 %. The median duration of response was 2.0 months, with a range of 0–16.0 months. During the study, five patients in the 7.5 mg cohort and one in the 12.5 mg cohort developed PD. The median PFS was 7.2 months across both groups.

Discussion

The PK and safety profiles of linifanib in combination with carboplatin and paclitaxel in patients with no prior chemotherapy for advanced non-squamous NSCLC support the use of the same dose and regimen for both Japanese and US patients. The PK similarity between these populations is consistent with those reported by Asahina and colleagues [16] in their phase 1 trial of linifanib monotherapy in Japanese patients in which they presented a post hoc analysis showing the similarity in PK among Japanese, non-Japanese Asian, and Caucasian patients. They reported average steady-state dose-normalized C_{max} of 0.028–0.036 μg/mL/mg and AUC_{24} of 0.37–0.52 μg h/mL/mg at 0.10–0.25 mg/kg linifanib dose in Japanese patients.

Also, in comparison with a similar US trial of linifanib combined with carboplatin/paclitaxel chemotherapy [18], PK parameters of linifanib are again comparable between Japanese and US subjects. In the US study, linifanib C_{max} was achieved in 3.4 h and the average dose-normalized steady-state C_{max} and AUC_{24} were 0.021 μg/mL/mg and 0.26 μg h/mL/mg, respectively, when linifanib was administered alone, comparing well with the same parameters in the present study and in the monotherapy trials within the variations normally seen. However, in the US trial, coadministration of linifanib with carboplatin/paclitaxel had no significant effect on the exposure of either linifanib or paclitaxel based on the point estimates of the ratios of central values of dose-normalized C_{max} or AUC of linifanib or paclitaxel. The similarities in linifanib PK in these monotherapy and combination studies in Japanese and non-Japanese subjects strongly suggest that linifanib is metabolized similarly in these populations. The observed effect of coadministration of linifanib with carboplatin/paclitaxel on linifanib pharmacokinetics in this study, and whether this interference is unique to Japanese patients or due to other reasons, remains a question to be assessed as part of future investigations with this regimen.

The antitumor effects seen in this study are generally similar to those previously reported in a phase 2 study evaluating this combination and performed with non-Japanese patients [17]. That study compared carboplatin/paclitaxel alone with carboplatin/paclitaxel plus linifanib (7.5 or 12.5 mg). The overall response rate was 31.9 % with the 12.5 mg linifanib dose versus 25.5 % with carboplatin/paclitaxel alone. PFS duration was 7.3 months with linifanib versus 5.4 months with carboplatin/paclitaxel alone. The rates of AEs tended to be lower than those observed in the current study. The findings of this study support those in the larger US trial and suggest that linifanib combined with carboplatin/paclitaxel is active and tolerable in patients with advanced/metastatic non-squamous NSCLC regardless of ethnicity. These results appear to confirm preclinical models suggesting that linifanib potentiates activity of carboplatin/paclitaxel [12, 13]. The predominant treatment-related toxicity in combination with carboplatin/paclitaxel was myelosuppression, as expected. Of note, there were no unexpected AEs, and only two patients experienced DLT. This safety profile was consistent with those of other anti-VEGF/VEGFR agents and with prior studies of linifanib [10].

The study established the tolerability and appropriate dose and regimen for further investigation of linifanib in combination with carboplatin/paclitaxel in Japanese patients with advanced NSCLC. Addition of linifanib to carboplatin/paclitaxel is a feasible first-line regimen in Japanese patients with advanced NSCLC. Further conclusions are prevented by the small number of patients and the lack of a control group, and further trials to evaluate this combination are warranted.

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Conflict of interest The design, study conduct, analysis, and financial support of the clinical trial were provided by AbbVie Inc. AbbVie participated in the interpretation of data, review, and approval of the content for publication. Authors M. McKee, D. Carlson, and H. Xiong are full-time AbbVie employees and may hold stock and/or stock options. Authors H. Horinouchi, N. Yamamoto, H. Nokihara, T. Horai, M. Nishio, F. Ohyanagi, A. Horiike, K. Nakagawa, M. Terashima, T. Okabe, H. Kaneda, and T. Tamura have no relevant conflicts.

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PHASE I STUDIES

Inhibition of EGFR, HER2 and HER3 signaling with AZD8931 alone and in combination with paclitaxel: Phase I study in Japanese patients with advanced solid malignancies and advanced breast cancer

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Summary *Background* AZD8931 is an equipotent, reversible inhibitor of signaling by epidermal growth factor receptor (EGFR), human EGFR 2 (HER2) and HER3. This two-part Japanese study (NCT01003158) assessed the safety/tolerability of AZD8931 monotherapy in patients with advanced solid tumors and in combination with paclitaxel in female patients with advanced breast cancer. *Methods* Monotherapy part: ascending doses of AZD8931 (40/60/80 mg twice daily [bid]) for 21 consecutive days. Combination part: AZD8931 40 mg bid and paclitaxel 90 mg/m^2 (on days 1, 8 and 15 of a 28-day cycle). *Results* Seventeen patients received AZD8931: 11 received AZD8931 monotherapy (40/60/80 mg [n=3/4/4]) and six AZD8931 40 mg bid plus paclitaxel. No dose-limiting toxicities were observed for AZD8931 alone or combined with paclitaxel. The most frequent adverse events (AEs) were diarrhea, paronychia, pustular rash and dry skin (each n=8) with AZD8931 monotherapy and diarrhea, stomatitis, rash, alopecia, epistaxis and neutropenia (each n=4) with combination therapy. Grade ≥3 AEs were reported for one, two and four patients in the 40 mg, 60 mg and combination groups, respectively. AZD8931 was rapidly absorbed with a half-life of 12 h. There was no evidence of pharmacokinetic interaction between AZD8931 and paclitaxel. Two patients (one in each part) had unconfirmed and confirmed partial responses, with a duration of 42 and 172 days, respectively. *Conclusion* Although maximum tolerated dose was not confirmed for AZD8931, based on overall incidence of rash and diarrhea AEs in the 80 mg group, doses up to 60 mg bid as monotherapy and 40 mg bid combined with paclitaxel are the feasible AZD8931 doses in Japanese patients.

Keywords AZD8931 · Paclitaxel · HER · Advanced solid tumors · Breast cancer

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Introduction

The human epidermal growth factor receptor (HER/erbB) family of receptor tyrosine kinases comprises epidermal growth factor receptor EGFR (erbB1), HER2 (erbB2), HER3 (erbB3) and HER4 (erbB4). Homodimerization and/or heterodimerization of these receptors activates intracellular signaling pathways involved in cell proliferation and survival

during normal physiological processes [1–6]. However, aberrant signal transduction via EGFR, HER2 and HER3 has been identified as a common component of multiple cancer types and appears to promote solid tumor growth [7–12]. For example, EGFR activation is seen in tumor types such as non-small cell lung cancer, breast, colorectal, and head and neck cancer, and over-expression of EGFR is observed in a proportion of breast, ovarian, bladder and gastric malignancies [10].

Targeting HER family members with small molecular agents, such as gefitinib and erlotinib, has demonstrated efficacy in EGFR-mutation-positive non-small cell lung cancer [13–15]. Similarly, lapatinib has shown efficacy in the management of HER2 over-expressing metastatic breast cancer [16]. Results from preclinical studies have suggested that EGFR inhibition enhances the antitumor activity of chemotherapeutic agents [17, 18]. In one Phase III study of 86 patients with HER2-positive breast cancer, the combination of lapatinib and paclitaxel led to statistically significant improvements in time to progression, event-free survival, objective response rate and clinical benefit rate compared with paclitaxel and placebo [19].

To date, development of agents that specifically target the HER receptor pathway has focused on inhibition of EGFR and/or HER2. However, there is increasing evidence that HER3 plays an important role in human tumorigenesis [7] due to its effect on phosphatidylinositol 3-kinase (PI3K) signal transduction, a known mediator of cancer cell survival and acquired resistance [13, 20]. As such, more complex and equipotent inhibition of signaling by the HER receptor family may provide greater antitumor activity [15].

AZD8931 is an orally bioavailable, reversible, tyrosine kinase, equipotent inhibitor of EGFR, HER2 and HER3 signaling [15]. The combination of AZD8931 with paclitaxel has shown synergistic cytotoxicity in breast cancer cell lines and xenograft models [21]. This two-part study was conducted to assess the safety and tolerability of multiple ascending doses of AZD8931 monotherapy in Japanese patients with advanced solid tumors and in combination with paclitaxel in female Japanese patients with advanced breast cancer.

Patients and methods

Study design and patients

This was a two-part (monotherapy and combination therapy), single-center, Phase I open-label study (clinicaltrials.gov: NCT01003158). The monotherapy part enrolled male or female Japanese patients aged ≥20 years with histologically or cytologically confirmed advanced solid malignancies that were refractory to standard therapies or for which no standard therapy existed. The combination part enrolled female Japanese patients aged ≥20 years with histologically or cytologically confirmed locally advanced or metastatic breast cancer who were ineligible for hormonal or anthracycline therapy.

Inclusion criteria in both parts included: World Health Organization performance status of 0–2; life expectancy ≥12 weeks; absolute neutrophil count ≥1.5 × 10^9/L or platelets ≥100 × 10^9/L and hemoglobin >9 g/dL; serum bilirubin <1.5 times the upper limit of normal (ULN), alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase (ALT) <2.5 x ULN (except in patients with liver or bone metastases); serum creatinine ≤1.5 x ULN or creatinine clearance ≥50 mL/min; cardiac ejection fraction higher than the institution's lower limit of normal range. Patients were excluded from both parts if they had a history of cardiovascular disease; resting electrocardiogram (ECG) with measurable QTc interval >450 ms at ≥2 time points within 24 h; medical diagnosis of acne rosacea, psoriasis or severe atopic eczema; any ocular disease or condition that was active or likely to be aggravated during treatment; poorly controlled clinical disorders (eg diabetes mellitus, hypercalcemia or other systemic condition) or previous/current evidence of brain metastasis, interstitial lung disease or spinal cord compression; anticancer therapy within 4 weeks of the start of study treatment (6 weeks for nitrosurea or mitomycin C) or concomitant medication with potent inhibitors/inducers of CYP3A4 or CYP2D6; anti-seizure medication or corticosteroids; unresolved adverse events (AEs; Common Terminology Criteria for Adverse Events [CTCAE] grade ≥2) from previous anticancer therapy, as well as hypersensitivity to previous therapy with oral tyrosine kinase inhibitors; known hypersensitivity to paclitaxel or progression of disease during or within 6 months of receiving previous paclitaxel treatment (combination part only).

All patients provided written informed consent. The study was approved by the Institutional Review Board of Kinki University, Osakasayama, Japan, and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and the AstraZeneca policy on bioethics [22].

Treatment

In the monotherapy part, patients in each dose cohort received a single oral dose of AZD8931 on day 1 (D1), followed by a 6-day observation period, and thereafter received AZD8931 twice daily (bid) for 21 consecutive days (R1–R21). The initial cohort received AZD8931 40 mg, followed by 60 mg and 80 mg in subsequent cohorts. Following review of AZD8931 data from a Caucasian Phase I study, 40 mg was considered the clinically feasible dose for long-term treatment; this was primarily based on the incidence of CTCAE grade 3 rash at doses of ≥80 mg, as well as CTCAE grade 3 diarrhea at doses ≥160 mg [23]. In the combination part, patients received AZD8931 bid (initial dose based on the maximum tolerated dose [MTD] determined in the monotherapy part) starting on

day 2 of a 28-day cycle, with paclitaxel 90 mg/m^2 administered on days 1, 8 and 15. Patients were able to continue treatment indefinitely if they did not meet a withdrawal criterion, were free from intolerable toxicity and were considered by the investigator to be receiving clinical benefit.

A minimum of three evaluable patients were to be dosed initially in each dose group in the monotherapy part. If no patient experienced a dose-limiting toxicity (DLT), dose escalation was permitted. If one patient experienced a DLT, additional patients were enrolled to a maximum of six; if no further patients experienced a DLT, enrollment into the next dose cohort was permitted. If ≥2 patients experienced a DLT, this dose was considered non-tolerated and the previous dose was defined as the MTD. The DLT evaluation period for the monotherapy part started from the first administration of AZD8931 and continued until R21 (within 28 days of the first dose); for the combination part, DLTs were evaluated for the first 28 days of cycle 1. In both parts, DLTs were defined as any of the following AEs or laboratory abnormalities considered related to AZD8931: clinically significant symptomatic ocular surface lesion; CTCAE grade 4 neutropenia or thrombocytopenia with a duration of ≥4 days; grade ≥3 neutropenia that was either associated with a body temperature of ≥38 °C and was unresponsive to antipyretics or required hospitalization; grade ≥3 thrombocytopenia associated with non-traumatic bleeding; grade ≥3 hyperkalemia or hyperglycemia; grade ≥3 events (that could not be attributable to other causes) of hypotension, urologic toxicity, clinically significant rash that despite optimal treatment remained grade ≥3, interstitial lung disease or pneumonitis, nausea, vomiting, or diarrhea; any other clinically significant grade ≥3 toxicity considered related to study drug; QTcF (Fridericia's correction) interval >500 ms or increased by >60 ms compared with baseline on two ECGs ≥30 min apart; symptomatic congestive cardiac failure associated with a decreased left ventricular ejection fraction (LVEF), or decrease in LVEF ≥20 % below the lower limit of the normal range; a delay of ≥7 days for paclitaxel administration on day 1 of cycle 2 as a consequence of AZD8931-induced toxicity (combination part only).

Objectives and assessments

The primary objectives were to assess the safety and tolerability of multiple ascending doses of AZD8931 (monotherapy part) and of AZD8931 in combination with paclitaxel (combination part). Safety and tolerability were assessed throughout the study by evaluation of AEs using CTCAE version 3, laboratory findings, physical examinations, vital signs, cardiac monitoring and ophthalmic assessments. Full ophthalmic assessments were performed at screening and at R21; beyond R21, a full examination was only required in the case of a clinically significant ophthalmic abnormality. Cardiac monitoring was performed using a 12-lead ECG at screening, D1–D5, R1, R3, R7, R14, R21 and every 3 weeks thereafter for the monotherapy part, and at screening, D1–D4, D15 and every 4 weeks from cycle 2 onwards for the combination part. High-resolution computed tomography and arterial oxygen saturation were mandatory and had to be performed at baseline and throughout the study.

Key secondary objectives were to identify the MTD of continuous AZD8931 bid monotherapy and continuous AZD8931 bid in combination with paclitaxel; to characterize the pharmacokinetic (PK) profile of AZD8931 under both treatment regimens; and to characterize the PK profile of paclitaxel. During monotherapy, blood samples were taken for PK analysis on D1 and R14 pre-dose, 1, 2, 4, 6, 8, 10 (prior to the second dose of AZD8931 on R14), 24 (D1 only), 48 (D1 only) and 72 (D1 only) hours post-dose. Additional samples were taken pre-dose on days R3 and R7. During combination therapy: blood samples were taken for AZD8931 PK analysis pre-dose, 1, 2, 4, 6, 8 and 10 h post-dose on days 7 and 8; samples for AZD8931 combined with paclitaxel PK evaluations were taken pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, 10 and 24 h (prior to AZD8931 dosing, day 1 only) post-dose on days 1 and 8. Plasma concentrations of AZD8931, *O*-desmethyl AZD8931 and paclitaxel were determined using high-performance liquid chromatography with mass spectrometry.

Preliminary efficacy of AZD8931 alone and in combination with paclitaxel was an exploratory objective. Tumor assessments were performed according to Response Evaluation Criteria in Solid Tumors (version 1.0) [24]. Baseline radiological tumor assessments were performed ≤4 weeks before the start of treatment, following 21 days of continuous multiple dosing and approximately every 6 weeks thereafter for AZD8931 monotherapy, or every 8 weeks for combination therapy, until withdrawal from the study. Optional exploratory objectives were to examine the relationship between exploratory biomarkers from blood and tumor tissue samples and clinical outcome, as well as pharmacogenetic analysis.

Statistical analysis

No formal statistical analyses were performed; therefore, data are summarized descriptively. The safety analysis set comprised all patients who received at least one dose of AZD8931. For inclusion in the DLT set, evaluable patients were defined as those who had received ≥75 % of the planned dose of AZD8931 within 28 days of the first dose (both study parts), and for the combination part had completed at least one cycle of weekly paclitaxel and all safety assessments or experienced a DLT during the DLT evaluation period. Patients with evaluable PK data were included in the PK analysis set. Patients who had received at least one dose of AZD8931 and for whom tumor response data were available were included in the efficacy analysis.

Results

Patient characteristics and disposition

Between January 2010 and November 2011, 27 patients were enrolled. Seventeen patients (11 in the monotherapy part and six in the combination part) received at least one dose of AZD8931 and were included in the safety and PK analysis set (Table 1). Sixteen patients were evaluable for efficacy as one patient in the monotherapy part discontinued the study after the first dose of study drug and no efficacy data were recorded. Sixteen patients completed the 28-day evaluation period and 14 remained on treatment after this period.

Safety and tolerability

There were no DLTs in either treatment part; therefore, the MTD of AZD8931 as monotherapy or in combination with paclitaxel could not be determined within the pre-specified dose ranges. Dosing for the combination part (AZD8931 40 mg plus paclitaxel) was selected based on the incidence of rash and diarrhea AEs observed in the monotherapy part and that observed for patients receiving AZD8931 in combination with paclitaxel in a Western population (Clinicaltrials.gov NCT00900627) [25].

The median actual duration of AZD8931 treatment was 43.5 days (range 1–239) for the monotherapy part and 79.5 days (range 53–244) for the combination part. The most frequently reported AEs were diarrhea, paronychia, pustular rash and dry skin during AZD8931 monotherapy, and diarrhea, stomatitis, rash, alopecia, epistaxis and neutropenia during combination therapy (Table 2). Two ophthalmic AEs (eyelid edema and punctate keratitis) were reported in the present study, both in the combination part.

In total, seven (41.2 %) patients had grade ≥3 AEs. Three patients receiving AZD8931 monotherapy had grade 3 AEs of anemia, intervertebral disc protrusion and cancer pain (n=1 each). Four patients receiving combination therapy had a total of six grade ≥3 AEs: grade 3 AEs were neutropenia (reported in two patients), leucopenia, peripheral sensory neuropathy and papular rash (reported in one patient each); grade 4 decreased neutrophil count was also reported in one patient. Only the papular rash event was considered related to AZD8931 treatment. Two patients had a serious AE (grade 3 intervertebral disc protrusion in the AZD8931 40 mg monotherapy cohort; grade 2 infectious pneumonia in the AZD8931 40 mg plus paclitaxel cohort); neither was considered to be related to study treatment. Only one AE, grade 1 pneumonia observed in a patient receiving AZD8931 40 mg bid in combination with paclitaxel, led to permanent treatment discontinuation; this event was considered by the investigator to be related to both AZD8931 and paclitaxel treatment. There were no findings of clinical concern for vital signs, ECGs, echocard-iogram or ophthalmological assessments, or for hematology or biochemical parameters.

Table 1 Patient demographics and baseline characteristics (safety population)

	AZD8931 monotherapy part				AZD8931 combination part
	40 mg bid (n=3)	60 mg bid (n=4)	80 mg bid (n=4)	Total (n=11)	40 mg bid + paclitaxel (n=6)
Median age, years (range)	58 (46–63)	54 (37–77)	64 (59–69)	59 (37–77)	54 (49–69)
Male/female, n	2/1	2/2	3/1	7/4	0/6
Primary tumor type, n (%)					
Breast	–	–	–	–	6 (100)
Colorectal	1 (33)	1 (25)	–	2 (18)	–
Lung	–	1 (25)	–	1 (9)	–
Skin/soft tissue	–	–	1 (25)	1 (9)	–
Stomach	–	1 (25)	1 (25)	2 (18)	–
Thyroid	–	–	1 (25)	1 (9)	–
Other	2 (67)	1 (25)	1 (25)	4 (36)	–
Previous cancer treatment, n					
Chemotherapy	3 (100)	4 (100)	4 (100)	11 (100)	6 (100)
Radiotherapy	1 (33)	1 (25)	4 (100)	6 (55)	6 (100)
Immunotherapy	–	1 (25)	–	1 (9)	–
Hormonal therapy	–	–	–	–	6 (100)