AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6244
Study Code	D1532C00004
Edition Number	1
Date	10 April 2013

A Phase I, Open-Label, Multi-center Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD6244 Hyd-Sulfate When Given in Combination with Standard Doses of Selected Chemotherapies to Patients with Advanced Solid Tumors

Study dates:	First patient enrolled: 14 December 2007 Data cut off: 20 August 2010 Last patient completed last visit: not applicable
Phase of development:	Clinical pharmacology (I)
International Co-ordinating Investigator:	Patricia LoRusso, DO Wayne State University, Karmanos Cancer Institute, Wertz Clinical Cancer Center, Detroit, MI 48201
Sponsor's Responsible Medical Officer:	Ian Smith, MD Medical Science Director, AstraZeneca, Parklands, Alderley Park, Macclesfield, Cheshire, UK, SK10 4TG

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

The study was conducted at 4 study centres in the United States (US). The first patient enrolled into the study on 14 December 2007.

Publications

None at the time of writing this report.

Objectives

Primary objectives:

To investigate the safety, tolerability, and pharmacokinetics (PK) of twice daily (BD) oral doses of AZD6244 Hyd-Sulfate when administered in combination with the following chemotherapies:

- Docetaxel
- Dacarbazine
- Erlotinib
- Temsirolimus

Secondary objectives:

- To define the highest tolerated dose of AZD6244 Hyd-Sulfate when administered in combination with standard doses of selected chemotherapies.

Exploratory objectives:

- To make a preliminary assessment of tumour response as measured by objective response rate (ORR) per investigator's assessment using Response Evaluation Criteria in Solid Tumors (RECIST) when AZD6244 Hyd-Sulfate was given in combination with standard doses of selected chemotherapies.
- To analyse biological samples (eg, archived tumour, plasma) for factors that may influence the sensitivity to AZD6244 Hyd-Sulfate (or agents used in combination), such as genetic variability, gene expression profiling and protein expression profiling. This objective will not be reported in this clinical study report (CSR).
- To collect a blood sample (optional) for DNA extraction and storage to provide data to investigate whether the variability (if observed) in the PK, safety, efficacy, or pharmacodynamic (PD) results could be explained by the differences in the patient's genotype. This objective will not be reported in this CSR.

Study design

This was a Phase I, open-label study to investigate the safety, tolerability and PK of BD oral doses of AZD6244 Hyd-Sulfate when administered in combination with standard doses of selected chemotherapies (docetaxel, dacarbazine, erlotinib, and temsirolimus) in patients with advanced solid tumours. The study comprised 4 treatment arms (1 for each combination of AZD6244 with the selected chemotherapies), and 2 parts within each treatment arm: Part A (dose escalation) and Part B (dose expansion). Part A determined the maximum tolerated dose (MTD) of AZD6244 in that combination, and Part B evaluated the safety and PK of MTD in 12 additional patients.

Target population and sample size

Patients 18 years or older with advanced solid tumours for whom the selected standard chemotherapy regimens represented a standard of care, or those who may have derived benefit from the combination therapies, and who also satisfied the inclusion and exclusion criteria for the selected chemotherapy treatments were considered for this study.

The planned sample size was at least 18 evaluable patients per treatment group recruited at the dose deemed to be the AZD6244 MTD in combination therapy. Actual sample size for each treatment arm was as follows: docetaxel - 35 total patients, with 28 receiving the MTD; dacarbazine - 25 total patients, with 18 receiving the MTD; erlotinib: 48 total patients, with 6 receiving the MTD; temsirolimus - 32 total patients, with 26 receiving the MTD.

Investigational product and comparator(s): dosage, mode of administration and batch numbers´

Investigational product AZD6244: supplied as Hyd-Sulfate 25-mg capsules, oral. Batch numbers 09-003369AZ, 09-006065AZ, and 10-02068AZ. Dose varied by treatment arm as follows:

(a) Docetaxel: 50 mg BD and 75 mg BD

(b) Dacarbazine: 50 mg BD and 75 mg BD

(c) Erlotinib: 50 mg BD, 75 mg BD, 50 mg once daily (QD), 100 mg QD, and 150 mg QD

(d) Temsirolimus: 50 mg BD and 75 mg BD

Docetaxel: 75 mg/m^2 intravenous (IV) infusion over 60 minutes on Day 1 of each 21-day cycle

Dacarbazine: 1000 mg/m^2 IV infusion over 60 minutes on Day 1 of each 21-day cycle

Erlotinib: 100 mg oral daily continuously starting on Cycle 1/Day 1

Temsirolimus: 25 mg IV infusion over 60 minutes on Days 1, 8, and 15 of each 21-day cycle

Duration of treatment

Patients could continue to receive AZD6244 and the prescribed chemotherapy until progression or as long as they did not experience a dose-limiting toxicity (DLT), and were, in the opinion of the investigator, continuing to derive benefit. Patients could also continue to receive AZD6244 alone after the standard chemotherapy had been completed if the investigator believed they were continuing to derive benefit from AZD6244 treatment. However, patients were not allowed to begin new chemotherapy, or other combinations of chemotherapy, while continuing to receive AZD6244 therapy

Criteria for evaluation - efficacy, PK, and pharmacogenetics (main variables)

Secondary:

Where the data allowed, the following PK parameters were determined following administration of chemotherapy alone, AZD6244 alone, and AZD6244 and chemotherapy together. Additional parameters could be determined if deemed appropriate.

- AZD6244: maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (t_{max}), area under the plasma concentration-time curve from zero to 12 hours post-dose ($AUC_{(0-12)}$)
- N-desmethyl AZD6244: C_{max}, t_{max}, $AUC_{(0-12)}$
- Chemotherapies: C_{max}, t_{max}, $AUC_{(0-12)}$

Exploratory:

- Preliminary assessment of tumour response by ORR per investigator's assessment using Response Evaluation Criteria in Solid Tumors (RECIST) when AZD6244 was given in combination with standard doses of selected chemotherapies.
- To analyse biological samples (eg, archived tumour, plasma) for factors that may influence the sensitivity to AZD6244 (or agents used in combination), such as genetic variability, gene expression profiling, protein expression profiling.
- To collect a blood sample (optional) for DNA extraction and storage to provide data to investigate whether variability (if observed) in the PK, safety, efficacy or PD results could be explained by differences in the patient's genotype.

For both of the latter 2 exploratory objectives, an archived tumour specimen and plasma sample could be obtained pre-dose from all consenting patients for assessment of Ras (which is a small GTPase that hydrolyses GTP into GDP and phosphate) and RAF (which is a proto-oncogene serine/threonine-protein kinase protein) mutation status. Other biomarkers could be assessed as driven by emerging biological understanding and could include analysis of genetic variability of response related genes, gene expression profiling, protein expression profiling, etc.

- An archived tumour specimen and plasma sample could be obtained pre-dose from all consenting patients for assessment of Ras and RAF mutation status. Other biomarkers could be assessed as driven by emerging biological understanding and could include analysis of genetic variability of response related genes, gene expression profiling, protein expression profiling, etc

Criteria for evaluation - safety (main variables)

Primary:

Incidence and intensity of adverse events (AEs) as graded by Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0), vital signs (including blood pressure, pulse rate, weight, and body temperature), electrocardiogram (ECG) parameters, multi-gated acquisition (MUGA) scan, echocardiography, clinical chemistry (including liver function tests), Brain Natriuretic Peptide (BNP), Troponin I, hematology, urinalysis, and ophthalmologic examinations.

Secondary:

Incidence of DLTs.

Statistical methods

All statistical analyses were the responsibility of Biostatistics at AstraZeneca, Wilmington. No formal statistical hypothesis testing was performed on the data from this study.

The PK parameters were derived using noncompartmental analysis. C_{max} and t_{max} were determined by visual inspection of the plasma concentration-time profiles. $AUC_{(0-12)}$ was calculated by the linear trapezoidal rule. Where more than 1 maximum occurred, the reported value was assigned to the first occurrence.

Three populations were defined for analysis: safety population, evaluable for dose escalation (Part A), and evaluable for PK analysis. The safety population included all patients who received a least 1 dose of study medication. The patients evaluable for dose escalation were a subset of the safety population that included all patients who received approximately 80% of the defined doses of AZD6244 in Cycle 1 and completed at least 28 days of therapy from Cycle 1/Day 1, provided PK data and had all safety evaluations performed, or experienced a DLT. The patients evaluable for PK analysis were a subset of the safety population that included all patients who provided docetaxel, dacarbazine, erlotinib, temsirolimus, AZD6244, and/or N-desmethyl AZD6244 concentration-time data.

Subject population

In total, 140 patients were recruited into this study from 4 centres in the US. Of these 140 patients, 7 were ongoing at the time of the data cut-off (20 August 2010), and as of 01 October 2012, 3 of those patients are still ongoing. These patients were continuing to receive their assigned treatment; however, per protocol, only serious adverse event (SAE)

information is collected for these patients. Summaries of the subject population by treatment arm are as follows:

Docetaxel arm:

- In total, 35 patients entered the docetaxel arm, and 28 of these patients received the MTD of 75 mg BD of AZD6244 in combination with docetaxel 75 mg/m^2 IV on Day 1 of each 21 day cycle.

- Overall (Parts A+B), the mean age was 58.9 years (range: 38 to 80 years); 60% of patients were male, and 94% of patients were White. Overall, 60% of patients had a World Health Organization (WHO) performance status (PFS) of 1 (restricted activity), and the most common primary tumour site was skin/soft tissue with approximately 31% of patients. Overall, 85.7% of patients had received previous chemotherapy and 51.4% had received previous radiotherapy. All but 1 of the 35 patients had received at least 1 previous systemic anticancer regimen, and the median number of previous regimens was lower in Part B (2.5 regimens) than in patients receiving AZD6244 75 mg BD in Part A (5 to 7 regimens).

Dacarbazine arm:

- In total, 25 patients entered the dacarbazine arm, and 18 of these patients received the MTD of 75 mg BD of AZD6244 in combination with dacarbazine 1000 mg/m^2 IV on Day 1 of each 21-day cycle.

- Overall (Parts A+B), the mean age in the AZD6244 + dacarbazine arm of the study was 57.1 years (range: 32 to 80 years); 60% of patients were male, and all patients were White. Overall, 52% of patients had a WHO PFS of 1 (restricted activity), and the most common primary tumour site was skin/soft tissue (68%). Overall, 72% of patients had received previous chemotherapy, and 52% had received previous radiotherapy.

Erlotinib arm:

- In total, 48 patients entered the erlotinib arm, and 6 of these patients received the MTD of 100 mg QD of AZD6244 in combination with erlotinib 100 mg oral daily.

- Overall (Parts A+B), the mean age in the AZD6244 + erlotinib arm of the study was approximately 59 years (range: 36 to 79 years); approximately 48% of patients were male, and approximately 92% of patients were White. Overall, 40% of patients had a WHO PFS of 1 (restricted activity), and the most common primary tumour site was colorectal with approximately 44% of patients. Overall, 92% of patients had received previous chemotherapy, and 46% had received previous radiotherapy.

Temsirolimus arm:

- In total, 32 patients entered the temsirolimus arm, and 26 of these patients received the MTD of 50 mg BD of AZD6244 in combination with temsirolimus 25 mg IV on Days 1, 8, and 15 of each 21-day cycle.

- Overall (Parts A+B), the mean age in the AZD6244 + temsirolimus arm of the study was approximately 57 years (range: 32 to 79 years); 50% of patients were male, and approximately 94% of patients were White. Overall, 38% of patients had a WHO PFS of 1 (restricted activity), and the most common primary tumour site was colorectal with approximately 34% of patients. Overall, 91% of patients had received previous chemotherapy, and 50% had received previous radiotherapy.

Summary of efficacy results

Overall, the ORR across all doses was greatest in the AZD6244 + docetaxel arm (20.0%), followed by the AZD6244 + dacarbazine arm (16.0%) and the AZD6244 + temsirolimus arm (3.4%), and was lowest in the AZD6244 + erlotinib arm (2.2%). The following are efficacy results by treatment arm:

Docetaxel arm: The ORR across all doses was 20.0% (6 of 30 patients). The ORR at the MTD of AZD6244 75 mg BD + docetaxel was 17.4% (4 of 23 patients), and the median duration of response was 328 days.

Dacarbazine arm: The ORR across all doses was 16.0% (4 of 25 patients). The ORR at the MTD of AZD6244 75 mg BD + dacarbazine was 22.2% (4 of 18 patients), and the median duration of response was 245.5 days.

Erlotinib arm: The ORR across all doses was 2.2% (1 of 46 patients). The ORR at the MTD of AZD6244 100 mg QD + erlotinib was 0% (0 of 6 patients).

Temsirolimus arm: The ORR across all doses was 3.4% (1 of 29 patients). The ORR at the MTD of AZD6244 50 mg BD + temsirolimus was 4.2% (1 of 24 patients).

Summary of pharmacokinetic results

There appeared to be a trend towards higher AZD6244 concentrations in the presence of erlotinib. Although there were small differences in AZD6244 exposure when administered with docetaxel and dacarbazine, no gross differences in exposure were observed. Dosing in combination with temsirolimus did not appear to impact the exposure of AZD6244.

There was little evidence of a change in the N-desmethyl AZD6244 PK profile in the presence of any of the chemotherapy regimes.

A trend towards higher erlotinib exposure was observed when administered in the presence of AZD6244. A slight increase in docetaxel exposure was also observed when administered in

the presence of AZD6244. No evidence of any change in the PK profile of dacarbazine or temsirolimus was observed when administered with AZD6244.

Summary of safety results

The overall AE profile at MTD for AZD6244 in combination with docetaxel, dacarbazine, erlotinib, and temsirolimus was largely consistent with the known toxicity of each treatment administered as monotherapy. No new unexpected toxicities were reported. The majority of all AEs were CTCAE Grade 1 or 2. The primary cause of death was disease progression, and the overall incidences of permanent discontinuations of study treatment due to AEs were low and toxicities were managed successfully through dose reductions and dose interruptions. There were no new findings of clinical concern for vital signs, ECGs, echocardiogram or ophthalmological assessments, or for haematology or biochemical parameters.

The following is a summary of safety by treatment group:

Docetaxel arm:

- Duration of AZD6244 exposure was similar across dose groups, with mean durations of approximately 6 months and ranging from 1 to 714 days.
- The proportion of patients with at least 1 dose reduction or dose interruption was similar across dose groups with the exception of the Part B 75 mg BD group, in which 6 of the 13 patients had a dose reduction and 4 of the 13 patients had at least 1 dose interruption. AEs were the main reason for dose interruption (12 of 14).
- The overall AE profile at MTD (AZD6244 75 mg BD) for patients on AZD6244 + docetaxel 75 mg/m^2 IV was largely consistent with the known toxicity of both treatments.
  - The most commonly reported AEs, regardless of causality, consisted of (decreasing order of frequency) diarrhoea, peripheral oedema, fatigue, nausea, vomiting, dermatitis acneiform, and neutropenia.
  - AEs of infection, febrile neutropenia, and dysgeusia occurred more frequently (in 71.4%, 17.1%, and 28.6% of patients, respectively) during combination treatment than might be expected from previous experience with either agent in monotherapy.
- One patient had AEs with a fatal outcome (febrile neutropenia and pneumonia; Part A 50 mg BD).
- AZD6244 75 mg BD with granulocyte-colony stimulating factor (G-CSF) primary prophylaxis was the MTD administered in combination with docetaxel 75 mg/m^2 in a heavily pretreated patient population.

- AZD6244 75 mg BD with G-CSF as required for supportive care was a feasible dose for administration in combination with docetaxel 75 mg/m^2 in the less heavily pretreated population enrolled in Part B.

Dacarbazine arm:

- Duration of AZD6244 exposure was much longer in both 75 mg BD dose groups, with mean durations of approximately 6 months and ranging from 29 to 488 days, than in the 50 mg BD group.
- The incidences of dose reductions and dose interruptions were similar across groups. AEs were the main reason for dose interruption (10 of 11).
- The overall AE profile at MTD (AZD6244 75 mg BD) for patients on AZD6244 + dacarbazine 1000 mg/m^2 IV was largely consistent with the known toxicity of both treatments.
  - The most commonly reported AEs, regardless of causality, consisted of (decreasing order of frequency) nausea, diarrhoea, fatigue, decreased appetite, dizziness, headache, and vomiting.
  - Concomitant dacarbazine chemotherapy provides an alternative explanation for the incidence of decreased appetite.
- One patient had AEs with a fatal outcome (dyspnoea exertional and malignant pleural effusion; Part A 50 mg BD).
- The incidence of AEs leading to discontinuation of study treatment was low and was recorded in only 1 patient (at MTD).

Erlotinib arm:

- Duration of AZD6244 exposure was relatively short in all of the dose groups, but was much longer in both 50 mg BD dose groups, with mean durations of approximately 3 months and ranging from 1 to 500 days, than in the 75 mg BD, 100 mg QD, and 150 mg QD dose groups.
- The incidences of dose reductions and dose interruptions were similar across groups. AEs were the main reason for dose interruption (10 of 13).
- The overall AE profile at MTD (AZD6244 75 mg BD) for patients on AZD6244 + erlotinib 100 mg oral was largely consistent with the known toxicity of both treatments.

  - The most commonly reported AEs, regardless of causality, consisted of (decreasing order of frequency) diarrhoea, decreased appetite, fatigue, dermatitis acneiform, nausea, peripheral oedema, and pyrexia.

- There were no AEs with fatal outcome; the primary cause of death was disease progression.

- The incidence of AEs leading to discontinuation of study treatment was low and was recorded in only 1 patient (at MTD).

Temsirolimus arm:

- Duration of AZD6244 exposure was similar across dose groups, with mean durations of approximately 4 months and individual durations ranging from 1 to 635 days.

- The incidences of dose reductions and dose interruptions were similar across groups. AEs were the main reason for dose interruption (7 of 9).

- The overall AE profile at MTD (AZD6244 50 mg) for patients on AZD6244 + temsirolimus 25 mg IV was largely consistent with the known toxicity of both treatments.

  - The most commonly reported AEs at MTD, regardless of causality, consisted of (decreasing order of frequency) nausea, fatigue, diarrhoea, mucosal inflammation, vomiting, decreased appetite, dermatitis acneiform, peripheral oedema, thrombocytopenia, and constipation.

  - Concomitant temsirolimus chemotherapy provides an alternative explanation for gastrointestinal symptoms including diarrhoea.

- There were no AEs with fatal outcome; the primary cause of death was disease progression.

- The incidence of AEs leading to discontinuation of study treatment was low; 4 patients (12.5%).

Conclusion(s)

- In total, 140 patients were recruited into this study from 4 centres in the US. Of these 140 patients, 7 were ongoing at the time of the data cut-off (20 August 2010) and, as of 01 October 2012, 3 of those patients were still ongoing. There were no protocol deviations affecting the interpretation of the results of the study, and none resulted in exclusion from any analyses in any of the 4 treatment arms.

- Sample sizes in each dose group within each treatment arm were small, leading to scattered differences among dose groups in demographic or baseline characteristics in some of the treatment arms; however, the combined Part A and Part B patients for the dose selected for Part B (or from Part B in the case of erlotinib), and the overall study population were representative of a heavily pretreated, advanced population in oncology.

- Overall, ORR was greatest in the AZD6244 + docetaxel arm (20.0%), followed by the AZD6244 + dacarbazine arm (16.0%) and the AZD6244 + temsirolimus arm (3.4%), and was lowest in the AZD6244 + erlotinib arm (2.2%).

- There appeared to be a trend towards higher AZD6244 concentrations in the presence of erlotinib. Although there were small differences in AZD6244 exposure when administered with docetaxel and dacarbazine, no gross differences in exposure were observed. Dosing in combination with temsirolimus did not appear to impact the exposure of AZD6244.

- There was little evidence of a change in the N-desmethyl AZD6244 PK profile in the presence of any of the chemotherapy regimes.

- A trend towards higher erlotinib exposure was observed when administered in the presence of AZD6244. A slight increase in docetaxel exposure was also observed when administered in the presence of AZD6244. No evidence of any change in the PK profile of dacarbazine or temsirolimus was observed when administered with AZD6244.

- The MTD of AZD6244 with the standard of care dose for each combination agent was established:

  - AZD6244 75 mg BD + docetaxel 75 mg/m^2 IV infusion over 60 minutes on Day 1 of each 21-day cycle

  - AZD6244 75 mg BD + dacarbazine 1000 mg/m^2 IV infusion over 60 minutes on Day 1 of each 21-day cycle

  - AZD6244 100 mg QD + erlotinib 100 mg oral daily continuously starting on Cycle 1/Day 1

  - AZD6244 50 mg BD + temsirolimus 25 mg IV infusion over 60 minutes on Days 1, 8, and 15 of each 21-day cycle

- The overall AE profile at MTD for AZD6244 in combination with docetaxel (75 mg BD), dacarbazine (75 mg BD), erlotinib (100 mg QD), and temsirolimus (50 mg BD) was consistent with the known toxicity of both treatments. The most

commonly reported AEs, regardless of causality for each combination, in decreasing order of frequency, were:

- AZD6244 75 mg BD + docetaxel 75 mg/m^2 IV: diarrhoea, peripheral oedema, fatigue, nausea, vomiting, dermatitis acneiform, and neutropenia.
- AZD6244 75 mg BD + dacarbazine 1000 mg/m^2 IV: nausea, diarrhoea, fatigue, decreased appetite, dizziness, headache, and vomiting.
- AZD6244 100 mg QD + erlotinib 100 mg oral: diarrhoea, decreased appetite, fatigue, dermatitis acneiform, nausea, peripheral oedema, and pyrexia.
- AZD6244 50 mg BD + temsirolimus 25 mg IV: nausea, fatigue, diarrhoea, mucosal inflammation, vomiting, decreased appetite, dermatitis acneiform, peripheral oedema, thrombocytopenia, and constipation.

- No new unexpected toxicities were reported. The majority of all AEs were CTCAE Grade 1 or 2.
- The primary cause of death was disease progression (2 patients with AEs with an outcome of death out of 21 deaths during this study).
- The overall incidences of permanent discontinuations of study treatment due to AEs were low and toxicities were managed successfully through dose reductions and dose interruptions.
- Laboratory, vital sign, ECG, and visual assessments showed no unexpected findings.

Date of the report

10 April 2013