AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1152
Study Code	D1531C00009
Edition Number	1
Date	11 September 2012

A randomised, open-label, multi-centre, 2-stage, parallel group study to assess the efficacy, safety and tolerability of barasertib (AZD1152) alone and in combination with low dose cytosine arabinoside (LDAC) in comparison with LDAC alone in patients aged ≥60 with newly diagnosed acute myeloid leukaemia (AML) who are considered unsuitable to receive intensive induction chemotherapy regimens

Study dates:	First patient enrolled: 22 July 2009 (Stage 1 and Transition Phase) Last patient last visit: 27 June 2011 (Stage 1 and Transition Phase)
Phase of development:	Therapeutic exploratory (II)/Therapeutic confirmatory (III)

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

Study centre(s)

This was a multicentre study conducted at 46 centres in 9 countries (Australia [3 centres], France [6], Germany [4], Italy [5], Japan [7], Romania [2], Spain [6], the United Kingdom [3], and the United States of America [10]).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary: Stage 1	**Primary**	
To make a preliminary assessment of the relative efficacy of AZD1152 monotherapy compared to LDAC by assessment of OCRR.	OCRR defined as the proportion of patients achieving a complete remission or confirmed complete remission with incomplete recovery of neutrophils or platelets.	Efficacy
Secondary: Stage 1	**Secondary**	
To assess the efficacy of AZD1152 monotherapy compared to LDAC, by assessment of OS, DoR, DFS and Time to Complete Response.	OS, DoR, DFS and Time to Complete Response.	Efficacy
To assess the effects of AZD1152 monotherapy compared to LDAC on patients' HRQoL and disease-related symptoms.	The main outcome variables for HRQoL were the Trial Outcome Index and Total FACT-Leu score. Two analyses were performed for disease related symptoms using the 'Additional Concerns' subscales of the FACT-Leu and FACIT-Fatigue.	PRO
To assess the effects of AZD1152 monotherapy compared to LDAC on the number of key healthcare cost-generating events.	Incidence of events such as: anaemia, thrombocytopenia, neutropenia, febrile neutropenia, sepsis, invasive fungal infection, interstitial lung diseases, stomatitis/dysphagia, rash and cachexia.	HEOR
To assess the effects of AZD1152 monotherapy compared to LDAC on the requirement for key healthcare interventions.	Intravenous antibiotic use, intravenous anti-fungal usage, blood product support and hospitalisations.	HEOR
To assess the safety and tolerability of AZD1152 monotherapy compared with LDAC.	AEs, vital signs, electrocardiogram parameters, clinical chemistry, haematology (including clotting parameters) and urinalysis.	Safety
To determine the population PK of AZD1152 and AZD1152 hQPA, and to assess the relationship between PK and measures of PD response, efficacy and AEs in patients with AML. This objective will be reported in an addendum to the clinical study report.	Parameters that best describe the PK of AZD1152 and AZD1152 hQPA, as a minimum total body clearance of drug from plasma and apparent volume of distribution. The relationship between AZD1152 hQPA plasma concentration or other parameters of exposure and measures of PD response, efficacy and AEs was to be explored.	PK/PD

AE Adverse event; AML Acute myeloid leukaemia; DFS Disease-free Survival; DoR Duration of Response; FACIT-Fatigue Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-Leu Functional Assessment of Cancer Therapy - Leukaemia Questionnaire; HEOR Health economics outcomes research; hQPA Hydroxy-quinazoline pyrazole anilide; HRQoL Health-related quality of life; LDAC Low dose cytosine arabinoside; OCRR Overall Complete Response Rate; OS Overall Survival; PD Pharmacodynamic(s); PK Pharmacokinetic(s); PRO Patient reported outcomes.
Note: There were 2 exploratory objectives for Stage 1 (PD and pharmacogenetics); no data are presented in the clinical study report. For Stage 2, primary (efficacy), secondary (efficacy, PRO, HEOR, safety and PK/PD) and exploratory (PD, HEOR and pharmacogenetics) objectives were specified.

Study design

This is an open label, 2-stage, randomised, parallel group study to assess the efficacy and safety of AZD1152 in patients aged ≥60 years with newly diagnosed acute myeloid leukaemia (AML) who are considered unsuitable to receive intensive induction chemotherapy regimens. The study has 3 parts: Stage 1, a Transition Phase and Stage 2. Stage 1 provided a preliminary assessment of the relative efficacy and tolerability of AZD1152 as monotherapy compared with low dose cytosine arabinoside (LDAC). Stage 2 was designed to determine the efficacy and tolerability of monotherapy AZD1152, and AZD1152 in combination with LDAC, compared with LDAC alone. Based on the strength of the Stage 1 data and, in particular, the uncertainty as to whether this would translate into an Overall Survival (OS) benefit of sufficient magnitude in the final analysis, a strategic decision was taken not to proceed to Stage 2 of study D1531C00009.

Target subject population and sample size

Eligible patients were male or female, ≥60 years of age with newly diagnosed AML considered unsuitable to receive intensive induction chemotherapy regimens (due to the presence of at least 1 of the following factors: World Health Organisation performance status >2, age ≥75 years, adverse cytogenetics or organ dysfunction arising from significant co-morbid conditions not directly linked to leukaemia).

In Stage 1, 45 patients were randomised (2:1 ratio) to receive either AZD1152 or LDAC. Assuming an Overall Complete Response Rate (OCRR; the proportion of patients achieving either complete remission [CR] or a confirmed complete remission with incomplete recovery of neutrophils or platelets [confirmed CRi]) of 18% for LDAC and 36% for AZD1152, there was a 73% probability of observing an improvement of at least 10% in OCRR. Data from the initial 45 patients were insufficient to make a recommendation for continuation to Stage 2 and thus data from the Transition Phase patients were added to the analysis (planned 75 patients; total 77 patients; 51 randomised to AZD1152 and 26 to LDAC). With this number of patients there was an 80% probability of observing at least a 10% difference in OCRR.

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

Table S2 Details of investigational product

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Barasertib (AZD1152)	Lyophile, 100 mg (1200 mg per cycle), continuous 7-day infusion, intravenous	AstraZeneca	F13353	70677B09, 72470H09, S09H01
Diluent	Diluent, 5 mL, continuous 7-day infusion, intravenous	AstraZeneca	F13412	60968F08, 72408A09

Commercially marketed LDAC was sourced centrally by AstraZeneca. In regions where local regulations did not allow this, LDAC was sourced locally on a case by case basis. The LDAC dose was 400 mg per cycle.

Duration of treatment

AZD1152 was administered as a continuous 7-day intravenous infusion, starting on Day 1 (0 hours) and finishing on Day 8 of the 28-day cycle. LDAC was administered twice daily by subcutaneous injection for 10 days, followed by 18 days of recovery before commencing the next cycle. Unless deemed inappropriate by the investigator, patients in both stages were expected to complete at least 3 cycles (12 weeks) of treatment. Further cycles of treatment could be given if, in the opinion of the investigator, the patient was continuing to receive benefit.

Statistical methods

The primary outcome variable for efficacy assessment was OCRR, defined as the percentage of patients achieving a CR or complete remission with incomplete recovery of neutrophils or platelets (CRi), which was confirmed at least 21 days after first being observed (confirmed CRi).

In Stage 1 (and the Transition Phase), the primary assessment of efficacy was performed on all patients who received study treatment (modified intention-to-treat [mITT] population). These data were summarised in tabular form, along with the difference in OCRR and associated 80% and 95% confidence intervals (CIs). Duration of Response (DoR) and Disease-free Survival (DFS) were summarised descriptively and using Kaplan-Meier curves. Time to Complete Response was summarised descriptively and graphically. OS was summarised using Kaplan-Meier curves. In addition to the protocol specified analysis of OCRR, OS was analysed as per the pre-specification in the statistical analysis plan, which was when approximately 75% of the 77 patients randomised to Stage 1 and the Transition Phase had died.

Subject population

In total 77 patients were randomised into Stage 1 and the Transition Phase in a 2:1 ratio (51 patients to AZD1152 and 26 patients to LDAC) at 46 centres in 9 countries globally. Of these, 74 patients received treatment; 48 patients in the AZD1152 group and 26 patients in the LDAC group. A total of 77 patients were included in the ITT analysis set and all 74 patients who received treatment were analysed in the mITT and safety analysis sets.

As of the data cut-off (27 June 2011), 17 patients were continuing in the study (12 in the AZD1152 group and 5 in the LDAC group), but none were still receiving treatment. As of June 2012, no patients were continuing in the study. Overall 69 patients actively discontinued study treatment prior to data cut-off; a lower percentage in the AZD1152 group (44 patients [86.3%]) than the LDAC group (25 patients [96.2%]). Five patients died without actively discontinuing study treatment (AZD1152 group: 4 patients [7.8%]; LDAC group: 1 patient [3.8%]).

The mean age in the total study population was 74 years and the majority of patients were male and White; all patients had newly diagnosed AML. The demographics and baseline characteristics of the patients who received study treatment were generally balanced between the treatment groups. However, some numerical differences between the treatment groups were observed, although the small number of patients, particularly in the LDAC group, needs to be taken into consideration. There were fewer male patients in the AZD1152 group (52.9%) versus the LDAC group (69.2%). Patients in the AZD1152 group had a slightly higher median age than the LDAC group (76.0 years versus 72.5 years, respectively) and more patients were ≥75 years of age in the AZD1152 group versus the LDAC group (64.7% versus 26.9%, respectively). In addition, a lower percentage of patients in the AZD1152 group (25.0%) had adverse cytogenetics (central data analysis) than in the LDAC group (36.4%). Numerical differences between the treatment groups were also noted for performance status. However, performance status of 0+1 versus 2+3 was balanced across the 2 groups (0+1 AZD1152 70.6% versus LDAC 69.2% and 2+3 AZD1152 29.4% versus LDAC 30.8%).

In general, the 2 treatment groups were well balanced and allowed a valid comparison of safety and efficacy, with the possible exception of the excess of "unknown" cytogenetics (no sample available for central analysis) in the AZD1152 group (29.4%) versus the LDAC group (15.4%), and in patients with poorer performance status (score of 3 for 5.9% and 15.4% of patients in the AZD1152 and LDAC groups, respectively).

Summary of efficacy results

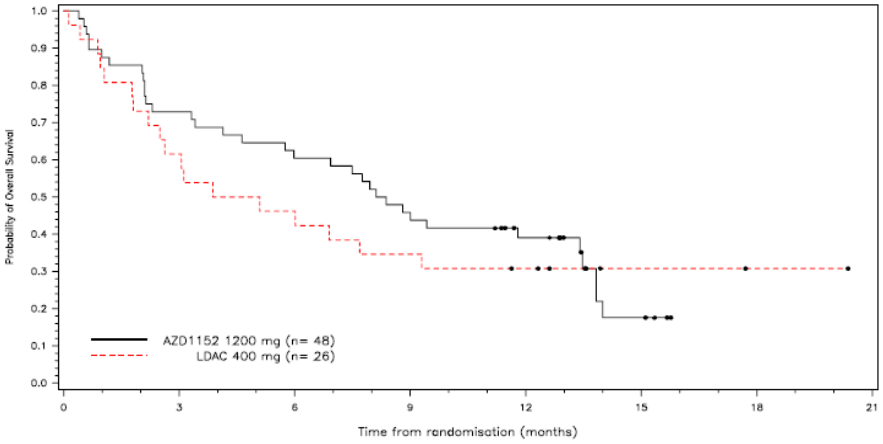
OCRR was measured by blinded central review. For the mITT population (primary analysis), 17 of 48 patients (35.4%) achieved CR/confirmed CRi in the AZD1152 group versus 3 of 26 patients (11.5%) in the LDAC group, translating to an absolute difference between the groups of 23.9% (80% CI: 10.6 to 34.8; 95% CI: 2.7 to 39.9). The 95% CI was distinct from zero indicating that the differences in response rates were statistically significant at the 5% level.

The responses in the AZD1152 group appeared to be durable (median DoR of 82 days). Median DFS for patients with a CR or confirmed CRi was 5.6 months in the AZD1152 group. There were too few responses in the LDAC group to draw a comparison of AZD1152 with LDAC. The majority of responses in the AZD1152 group and 2 of the 3 responses in the LDAC group occurred after either the first or second cycle of treatment. Responses were observed in all 3 cytogenetic risk groups.

Median follow-up for all patients (time to death or censoring) was 6.9 months. Median follow-up for the patients who were alive was 12.9 months in the AZD1152 group and 13.6 months in the LDAC group. The minimum follow-up for patients who were alive was approximately 11 months.

The HR for OS for the mITT population was 0.88 in favour of AZD1152; 95% CI: 0.49 to 1.58; 80% CI: 0.60 to 1.29 (see Figure S1). There were 34/48 (70.8%) deaths in the AZD1152 group versus 18/26 (69.2%) deaths in the LDAC group. Median OS was 8.2 months in the AZD1152 group and 4.5 months in the LDAC group.

Figure S1 Overall survival (mITT analysis set)



Number of patients at risk•

Month	000	003	006	009	012	015
AZD1152 1200 mg	48	035	029	022	015	004
LDAC 400 mg	26	016	012	009	007	002

• The number of patients at risk denotes the number of patients alive at the beginning of the period.

Quality of life and health economics outcomes research

In Stage 1 and the Transition Phase, at the end of Cycle 1, a higher proportion of patients reported a worsening in their symptoms, a worsening in their health-related quality of life (HRQoL), and bleeding easily in the AZD1152 group compared with the LDAC group. However, the number of patient studied was small and there was low overall compliance for the completion of questionnaires, which means the results reported need to be interpreted with caution.

There was no clear association between patient reported outcomes (PRO) response and OCRR.

Analysis of key healthcare cost-generating events showed a total of 77.1% of AZD1152 patients versus 23.1% of LDAC patients had stomatitis/mucositis (grouped terms) and 66.7% of AZD1152 patients versus 23.1% of LDAC patients had febrile neutropenia (grouped terms). There was a higher incidence of sepsis reported in the AZD1152 group (12.5%) versus the LDAC group (3.8%), and rates of neutropenia were also higher in the AZD1152 group (14.6%) versus the LDAC group (7.7%). Overall, 78.4% of AZD1152 patients required intravenous antibiotics and/or anti-fungals versus 53.8% of LDAC patients. The need for blood and related products was similar in the 2 groups (92.2% of AZD1152 patients and 100% of LDAC patients). The median number of days on treatment with an overnight stay in hospital (including the 28-day follow-up period) was 34 days for the AZD1152 group (including the hospital-based 7-day infusion) versus 19 days for the LDAC group, although wide variation was observed.

Summary of pharmacokinetic results

These data will be reported in an addendum to the clinical study report.

Summary of pharmacodynamic results

Any analysis of pharmacodynamic data will be reported at a later date.

Summary of pharmacokinetic/pharmacodynamic relationships

These data will be reported in an addendum to the clinical study report.

Summary of pharmacogenetic results

Any data from pharmacogenetic analyses will be reported at a later date.

Summary of safety results

In Stage 1 and the Transition Phase, all 74 patients treated had at least 1 adverse event (AE). The most common were stomatitis (70.8%), febrile neutropenia (66.7%), diarrhoea (50.0%), constipation (45.8%), nausea (43.8%) and vomiting (33.3%) with AZD1152, and nausea (38.5%), asthenia (30.8%), constipation (30.8%) and pyrexia (30.8%) with LDAC. More patients in the AZD1152 group had a Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher AE (83.3%) versus the LDAC group (69.2%). The most common were febrile neutropenia (50.0%), stomatitis (27.1%), and pneumonia (22.9%; including lobar pneumonia) with AZD1152, and anaemia (15.4%), dyspnoea (15.4%) and thrombocytopenia (15.4%) with LDAC.

There were 34 (70.8%) deaths with AZD1152 versus 18 (69.2%) with LDAC. Six patients in the AZD1152 group and 3 patients in the LDAC group died due an AE alone; however, none were considered by the reporting investigator to be related to treatment with the exception of an event of sepsis in the LDAC group. The 30-day mortality rate (all deaths) was similar in both treatment groups (AZD1152: 12.5%; LDAC: 15.4%). The 60-day and 90-day mortality rate was numerically lower in the AZD1152 group versus the LDAC group.

More patients in the AZD1152 group (47.9%) had a serious adverse event (SAE) than the LDAC group (38.5%). The most common with AZD1152 were pneumonia (12.5%; including lobar pneumonia), febrile neutropenia (10.4%), pyrexia (8.3%), stomatitis (6.3%), and neutropenia (4.2%). The only SAE reported in more than 1 patient with LDAC was pneumonia (7.7%). A similar low percentage of patients in the AZD1152 group (8.3%) and the LDAC group (7.7%) had an AE leading to discontinuation.

As expected, more patients in the AZD1152 group (95.8%) had an AE of special interest (alopecia, febrile neutropenia, stomatitis/mucositis, diarrhoea, nausea, and vomiting) than the LDAC group (61.5%). In total, 77.1% of patients in the AZD1152 group and 23.1% of patients in the LDAC group had an AE of stomatitis/mucositis (grouped terms), and 66.7% of patients in the AZD1152 group and 23.1% of patients in the LDAC group had an AE of febrile neutropenia (grouped terms). Alopecia, diarrhoea, nausea and vomiting were reported

by 11 (22.9%), 24 (50.0%), 21 (43.8%) and 16 (33.3%) patients in the AZD1152 group, respectively and by 0, 3 (11.5%), 10 (38.5%) and 5 (19.2%) patients in the LDAC group, respectively.

The majority of the events of stomatitis/mucositis resolved (on continued treatment or after treatment withdrawal), only 2 patients (4.2%) had a dose reduction due to an AE of stomatitis/mucositis, and no patients discontinued treatment due to stomatitis/mucositis.

Febrile neutropenia was more frequent and severe in the AZD1152 group (66.7% of patients had an AE [grouped terms]; 10.4% of patients had an SAE [grouped terms]) compared with the LDAC group (23.1% patients had an AE [grouped terms]; 7.7% of patients had an SAE [grouped terms]). Predose levels of CTCAE Grade 3 and 4 neutropenia were higher in AZD1152-treated patients (81%) than in LDAC-treated patients (62%).

There was an imbalance in the incidence and severity of infection type events, and in particular pneumonia, between the 2 treatment groups (CTCAE Grade 3 or higher: 22.9% in the AZD1152 group versus 7.7% in the LDAC group).

Both treatment groups had uniformly low red cell indices and haemoglobin on study entry, which fell slightly and cyclically across both treatment groups. Most patients in both treatment groups also had falls in the levels of platelets and neutrophils. A fall in leucocytes (and lymphocytes) was more profound and cyclical with treatment in the AZD1152 group than the LDAC group. CTCAE Grade 3 and Grade 4 values in haematological parameters (anaemia, leucopenia, neutropenia and thrombocytopenia) were observed in both treatment groups, as would be expected. Neutropenia was more frequently observed in AZD1152-treated patients and appeared to be associated with a deeper nadir compared with LDAC-treated patients. There was no clinically significant effect of either AZD1152 or LDAC on liver function and neither drug appeared to have a clinically significant effect on renal function. Other than febrile neutropenia, neutropenia, leucopenia, lymphopenia and thrombocytopenia (the latter is an acknowledged adverse reaction with cytosine arabinoside), there were no consistent clinically relevant trends in other clinical laboratory parameters, and myelosuppression was manageable with growth factor and blood product support.

Neither AZD1152 nor LDAC appeared to have a clinically significant effect on blood pressure or pulse rate. A review of the data did not reveal any underlying cardiac safety concerns, eg, QT interval corrected for heart rate and in general, the cardiac safety profile was consistent with an elderly population with AML. Adverse events in the cardiac system organ class appeared to be more frequent in the AZD1152 group (25.0%) than in the LDAC group (7.7%). However, many of the events were reported in the same patient or a long time after the end of treatment.

Summary of Findings (Stage 1 and the Transition Phase)

- Evidence of clinical activity of AZD1152 1200 mg has been shown through a statistically significant improvement in the primary endpoint of OCRR.
  - For the mITT population (primary analysis), 17 of 48 patients (35.4%) achieved CR/confirmed CRi in the AZD1152 group versus 3 of 26 patients (11.5%) in the LDAC group, translating to an absolute difference between the groups of 23.9% (80% CI: 10.6 to 34.8; 95% CI: 2.7 to 39.9).
- Responses to AZD1152 were seen in all 3 cytogenetic risk groups.
- There was a numerical improvement in OS in favour of AZD1152, with wide CIs:
  - HR: 0.88; 95% CI: 0.49 to 1.58; 80% CI: 0.60 to 1.29; there were 34/48 (70.8%) deaths in the AZD1152 group versus 18/26 (69.2%) deaths in the LDAC group;
  - Median OS for the mITT population was 8.2 months in the AZD1152 group and 4.5 months in the LDAC group.
- The responses in the AZD1152 group appeared to be durable (DoR and DFS) and the majority of responses occurred after either the first or second cycle of treatment.
- The safety profile was consistent with that known for AZD1152 monotherapy and with the known events described within the prescribing information for LDAC. However, the data indicate AZD1152 poses a greater toxicity burden than LDAC.
  - There were no new toxicities or evidence of cumulative toxicities with AZD1152; however, there was a greater incidence of febrile neutropenia and stomatitis requiring treatment compared with LDAC;
  - Despite the increased tolerability burden from AZD1152, the rate of discontinuation of treatment due to AEs in the AZD1152 group was low and similar compared with LDAC, and the rate of dose reduction in the AZD1152 group was low;
  - The rate of early mortality was low and similar in both treatment groups;
  - Overall the increased tolerability burden of AZD1152 appears acceptable given the increased benefit that was observed.
- At the end of Cycle 1, a higher proportion of patients reported a worsening in their symptoms, a worsening in their HRQoL, and bleeding easily in the AZD1152 group compared with the LDAC group. However, the small number of patients and low

overall compliance for the completion of questionnaires means the results reported after Cycle 1 need to be interpreted with caution.

- There was no clear association between best overall PRO response and OCRR.
- Substantial differences between the treatment groups in favour of LDAC in rates of key healthcare cost generating events were observed (eg, stomatitis/mucositis, febrile neutropenia and antibiotic/antifungal use). The median number of days spent in hospital was higher for patients receiving AZD1152 compared with patients receiving LDAC.
- Based on the strength of the Stage 1 data and, in particular, the uncertainty as to whether this would translate into an OS benefit of sufficient magnitude in the final analysis, a strategic decision was taken not to proceed to Stage 2.