AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Selumetinib (AZD6244)
Study Code	D1532C00006
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A Phase II, Double-Blind, Randomised Study to Assess the Efficacy of AZD6244 (Hyd-Sulfate) in Combination with Dacarbazine Compared with Dacarbazine Alone in First Line Patients with *BRAF* Mutation Positive Advanced Cutaneous or Unknown Primary Melanoma

Study dates: First subject enrolled: 2 July 2009
Last subject enrolled: 29 March 2010

Phase of development: Therapeutic exploratory (II)

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

Selumetinib is referred to as AZD6244 throughout this document.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives are presented in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the efficacy in terms of Overall Survival of AZD6244 in combination with dacarbazine, compared with dacarbazine alone, in first-line patients with *BRAF* mutation-positive advanced cutaneous or unknown primary melanoma	- Overall Survival
Secondary	Efficacy	To further assess the efficacy of AZD6244 in combination with dacarbazine, compared with dacarbazine alone, in first-line patients with *BRAF* mutation-positive advanced cutaneous or unknown primary melanoma	- Progression-Free Survival - Objective Response Rate - Duration of Response - Change in Tumour Size at 12 weeks - Alive and Progression-Free at 6 months
	Safety	To assess the safety and tolerability profile of AZD6244 in combination with dacarbazine	- Adverse Events - Clinical chemistry, haematology and urinalysis - Vital signs (including weight) - Physical examination - Echocardiogram - Electrocardiogram - Ophthalmologic examination
	Biomarker analysis	To investigate the use of plasma and serum as a potential source of circulating free tumour DNA for the analysis of *BRAF* mutation status.	Correlation of *BRAF* mutation status derived from plasma, serum, and tumour material.
Exploratory	Efficacy	To assess the prevalence, severity and change over time of advanced cutaneous or unknown primary melanoma specific symptoms in patients receiving AZD6244 in combination with dacarbazine and dacarbazine alone.	Total Melanoma Specific Symptom questionnaire score.

BRAF v-raf murine sarcoma viral oncogene homolog B1; DNA deoxyribonucleic acid
Refer to the Clinical Study Report (CSR) for secondary biomarker and pharmacokinetic objectives, and for the other exploratory objectives.

Study design

This was a Phase II, double-blind, randomised, placebo-controlled study comparing the efficacy of AZD6244 (75 mg twice daily [bd], orally uninterrupted) in combination with dacarbazine (1000 mg/m^2 intravenous [iv] infusion over at least 60 minutes on Day 1 of each

21-day cycle) versus dacarbazine alone, in first-line patients with v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutation-positive advanced (inoperable Stage III or IV) cutaneous or unknown primary melanoma. Patients were selected on the basis of *BRAF* mutation-positive status of their tumour sample and were randomised in a ratio of 1:1 to receive AZD6244 or placebo in combination with dacarbazine.

Target subject population and sample size

Male and female first-line patients aged 18 and over, with *BRAF* mutation-positive advanced (inoperable stage III and stage IV) cutaneous or unknown primary melanoma for whom dacarbazine was an appropriate therapeutic option were enrolled. Approximately 80 patients (40 per treatment group) were to be randomised into this study. The primary endpoint was overall survival (OS) and OS analysis was planned at 58 deaths. If the true hazard ratio (HR) was 0.57, this analysis would have at least 80% power to demonstrate a statistically significant difference for OS, assuming a 1-sided 10% significance level. In total, 91 patients were randomised.

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

AZD6244 and matching placebo Hyd-Sulfate formulation capsules were supplied in high-density polyethylene bottles. Patients received 3 x 25 mg AZD6244 capsules or 3 matching placebo capsules bd. The capsules were to be taken whole orally with approximately 240 mL water on an empty stomach.

In case of any intolerable AE, the investigator applied dose reduction/adjustment in 3 allowed steps: 75 mg bd (initial dose) to 75 mg once daily (qd) (the first reduction) to 50 mg bd (the dose adjustment) to 50 mg qd (the final dose reduction).

Dacarbazine was sourced locally, or prescribed according to local regulations. Dacarbazine 1000 mg/m^2 was administered iv over at least 60 minutes on Day 1 of each 21-day cycle.

Individual batch numbers and further information are included in the clinical study report.

Duration of treatment

Patients received AZD6244 75 mg or matching placebo bd orally uninterrupted until Response Evaluation Criteria In Solid Tumours (RECIST)-defined disease progression, in the absence of significant toxicity.

Patients were expected to receive up to 8 cycles of dacarbazine in the absence of significant toxicity. Investigators could reduce the number of cycles of dacarbazine if significant toxicity developed. Further cycles of dacarbazine could be administered at the investigator's discretion if considered beneficial and it did not contravene local practice.

Statistical methods

The primary objective of this study was to compare the efficacy of AZD6244 in combination with dacarbazine, versus dacarbazine alone, in first-line patients with *BRAF* mutation-positive advanced cutaneous or unknown primary melanoma, by assessing OS. OS was analysed using a Cox proportional hazards model allowing for the effect of treatment and adjusting for World Health Organisation (WHO) performance status (PS), lactate dehydrogenase (LDH), metastatic status (M1c vs other), and histopathological type (superficial spreading melanoma [SSM] vs other). The HR for treatment was estimated together with its 80% profile likelihood confidence interval (CI) and 1-sided p-value (a HR <1 would favour AZD6244 in combination with dacarbazine).

The secondary objective of this study was to compare the efficacy of AZD6244 in combination with dacarbazine, versus dacarbazine alone, by assessing the secondary variables of progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), change in tumour size at 12 weeks, and proportion of patients alive and progression-free at 6 months (APF6). RECIST measurements were used to derive the secondary variables of PFS, ORR, DoR, and change in tumour size. All RECIST assessments were performed using modified RECIST version 1.0.

The study included 4 main analysis populations: Intention-to-treat (ITT), per-protocol (PP), safety, and pharmacokinetic (PK). The primary analysis population was the ITT population.

Subject population

The first patient was randomised on 20 July 2009, the last patient was randomised on 08 April 2010, and the data cut-off (DCO) date for the study was 20 November 2011.

Of the 385 patients screened, 91 patients were randomised (45 patients to receive AZD6244+dacarbazine and 46 patients to receive placebo+dacarbazine). One patient from each group was randomised but did not receive the randomised treatment and was therefore, excluded for safety and PP analyses. All patients who received the randomised treatment also received dacarbazine.

All patients were White. The mean age of patients in the 2 treatment groups was 53.6 years (ranging from 18 to 84 years), with a higher number of patients in the ≤65 years age group.

The 2 treatment groups were generally well balanced at baseline with respect to important demographic and baseline characteristics, with the exception of histology, gender, and previous medications. A statistical model, adjusting for all the potentially imbalanced baseline characteristics, did not influence the interpretation of the primary endpoint (data on file).

The concomitant medications administered during the study were representative of those commonly prescribed for patients with melanoma, the expected AE profiles for AZD6244 and dacarbazine as monotherapy, and/or other co-morbidities commonly seen in patients with melanoma.

Consistent with the population intended by the protocol, patients who participated in this study were representative of first-line patients with *BRAF* mutation-positive advanced cutaneous or unknown primary melanoma.

Efficacy

Primary Variable: Overall Survival

This Phase II study showed an improvement in OS that did not reach statistical significance (HR 0.93, 80% CI [0.67, 1.28], 1-sided p-value 0.3873, 66 events). The median OS was 424 days (13.9 months) in the AZD6244+dacarbazine group compared to 321 days (10.5 months) in the placebo+dacarbazine group (Table S2).

Table S2 Summary of primary analysis of Overall Survival – ITT analysis set

			Randomised Treatment Comparison				
Randomised Treatment	**N**	**_Events_ Number (%)**	**Hazard ratio**	**80% CI**	**1-sided p-value**	**95% CI**	**2-sided p-value**
AZD6244 75 mg BD + Dacarbazine	45	31 (68.9)	0.93	(0.67, 1.28)	0.3873	(0.57, 1.52)	0.7747
Placebo BD + Dacarbazine	46	35 (76.1)					

The analysis was performed using Cox proportional hazards model.
The model allowed for the effect of treatment and included term for WHO PS, LDH, M status, and tumour sub-type.
A Hazard Ratio <1 favours AZD6244 + Dacarbazine
BD Twice daily; CI Confidence interval; ITT Intention-to-treat.

The Kaplan-Meier curves largest separation is at the median and subsequently, the median difference was not representative of the treatment difference over time. Proportional hazards were observed.

The results of sensitivity analysis to assess OS in PP population were consistent with those of the primary ITT analysis (HR 0.93, 80% CI [0.67, 1.29]; 1-sided p-value 0.3956).

The treatment difference was consistent within the levels of the primary covariates (WHO PS, LDH, M status [M1c vs other] and histopathological type [SSM vs other] as well as gender and age) and a global interaction test was not significant (2-sided p-value 0.764). Differences in the treatment effect were observed according to gender suggesting a better treatment effect in female patients. However, there is no scientific rationale for females to respond better than males. An additional global interaction test adding; gender, age, gender by treatment, and age by treatment to the primary global test covariates, was not statistically significant (2-sided p-value 0.2151) (data on file) so this has not been investigated further.

Secondary Variables

By the DCO date of 20 November 2011, a total of 87 progression events had occurred: 42 in the AZD6244+dacarbazine group and 45 patients in the placebo+dacarbazine group. The majority (91.2%) of events in both the treatment groups were due to RECIST-defined progression.

Progression-free Survival

The addition of AZD6244 to dacarbazine produced a statistically significant improvement in PFS as compared with dacarbazine alone (HR 0.63, 80% CI [0.47, 0.84], 1-sided p-value 0.021); equating to a 37% reduction in the risk of progression. Proportional hazards were observed. The sensitivity analyses performed were consistent with the primary analysis for PFS.

Objective Response Rate

The primary analysis of ORR demonstrated the required level of promising activity ($p<0.1$, 1-sided) (OR 1.95, 80% CI [1.06, 3.66], 1-sided p-value 0.0809). One patient in each treatment group experienced a complete response (this was a confirmed complete response in the AZD6244+dacarbazine group). Partial response was observed in 17 (37.8%) patients in the AZD6244+dacarbazine group of which, 12 (26.7%) patients had confirmed response and 5 (11.1%) patients had unconfirmed response. There were 11 (23.9%) patients with partial responses in the placebo+dacarbazine group of which, 6 (13.0%) responses were confirmed and 5 (10.9%) responses were not confirmed.

Duration of Response

The median DoR was longer in the AZD6244+dacarbazine group (168 days [5.5 months]) as compared with the placebo+dacarbazine group (124 days [4.1 months]).

The ratio of the expected DoR (EDoR) between the treatment groups also demonstrated the required level of promising activity (1-sided $p<0.1$), (EDoR ratio 1.88, 80% CI [1.08, 3.26], 1-sided p-value 0.071). The EDoR for patients in the AZD6244+dacarbazine group was 84.9 days (2.8 months) compared with 45.2 days (1.5 months) for patients in the placebo+dacarbazine group.

Change in Tumour Size

A non-parametric analysis was performed as the primary method, due, primarily, to a large imputed value resulting in an extreme outlier. The change in tumour size at Week 12 was numerically better in the AZD6244+dacarbazine group however, the difference was not significant (Hodges Lehmann Estimate -13.4%, 80% CI [-24.95, -1.59], 1-sided p-value 0.2141).

Alive and Progression-Free at 6 months

Consistent with the PFS results, the difference in APF6 demonstrated the required level of promising activity (p-value <0.1) (HR 0.60, 80% CI [0.42, 0.85], 1-sided p-value 0.0298).

Patient-reported outcomes/quality of life

A baseline and at least 1 post-baseline Melanoma specific symptom questionnaire (MSSQ) was completed by 93.2% of patients from the AZD6244+dacarbazine group and 95.6% of patients from the placebo+dacarbazine group. Compliance rates for questionnaire completion remained at ≥60% until Week 33 in both treatment groups. The evaluability rate of completed forms ranged from 91.7% to100% at all visits.

Both the time to deterioration in Melanoma Subscale (MS) (HR 1.27, 80% CI [0.87, 1.88], 2-sided p-value 0.4165), and MS improvement rates (OR 0.86, 80% CI [0.46, 1.59], 1-sided p-value 0.6220) numerically favoured the placebo+dacarbazine group; the differences were not statistically significant.

Summary of safety results

The safety analysis set included 89 patients who received at least 1 dose of AZD6244/placebo in combination with dacarbazine (44 in the AZD6244+dacarbazine group and 45 in the placebo+dacarbazine group).

The median actual duration of AZD6244/placebo treatment was longer in the AZD6244+dacarbazine group as compared with the placebo+dacarbazine group (175 vs 105 days).

The incidence of AEs of CTCAE grade ≥3 (68.2% vs 42.2%), SAEs (50.0% vs 17.8%), AEs leading to hospitalisation (36.4% vs 13.3%), and AEs leading to discontinuation (15.9% vs 4.4%) was higher in patients in the AZD6244+dacarbazine group as compared with the placebo+dacarbazine group. The incidence of AEs leading to death reported in this study was similar between the AZD6244+dacarbazine (68.2%) and placebo+dacarbazine (75.6%) groups. The differential tolerability profile did not result in a greater number of AEs leading to death, which was low (and also attributed to disease progression in the majority of these patients) for both treatment groups (2.3% vs 4.4%). The majority of the AEs reported in this study were CTCAE grade 1 or 2.

The most commonly reported AEs (reported in >35% of patients in the AZD6244+dacarbazine group) were nausea (63.6% vs 55.6% in the placebo group), dermatitis acneiform (52.3% vs 2.2%), diarrhoea (47.7% vs 28.9%), vomiting (47.7% vs 33.3%), asthenic conditions (grouped term) (63.6% vs 51.1%), and fluid retention (grouped term) (54.5% vs 11.1%). With the exception of nausea, these AEs also occurred more commonly in the AZD6244+dacarbazine group than in the placebo+dacarbazine group.

There was a higher incidence of patients with a reduction from baseline in platelet counts (47.7% vs 35.6%, predominantly 1-grade reductions) and asymptomatic reversible decreases in LVEF (20.5% vs 11.4%) in the AZD6244+dacarbazine group than in the placebo+dacarbazine group. The safety findings in this study were broadly consistent with an additive combination of the known monotherapy profiles of AZD6244 and dacarbazine.