A Phase II, Open-Label, Randomized Study to Assess the Efficacy and Safety of AZD6244 (ARRY-142886) Versus Pemetrexed in Patients with Non-small Cell Lung Cancer Who Have Failed One or Two Prior Chemotherapeutic Regimens

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Introduction: AZD6244 (ARRY-142886) is a potent, selective MEK inhibitor. This study aimed to evaluate the efficacy and safety of AZD6244 versus pemetrexed as second- or third-line treatment in patients with advanced non-small cell lung cancer (NSCLC).

Methods: In this randomized phase II study, patients received either 100 mg oral AZD6244 free-base suspension twice daily or 500 mg/m^2 intravenous pemetrexed once every 3 weeks after pretreatment with a corticosteroid, folic acid, and vitamin B12. The primary end point of the study was the disease progression event count.

Results: Eighty-four patients were randomized. Disease progression events were experienced by 28 (70%) and 26 (59%) patients in the AZD6244 and pemetrexed groups, respectively. Median progression-free survival was not statistically significantly different between the AZD6244 and pemetrexed groups (67 versus 90 days, respectively; hazard ratio 1.08, two-sided 80% confidence interval = 0.75–1.54; $p = 0.79$). Two patients in the AZD6244 group had a best response to treatment of partial response. In the pemetrexed group, one patient achieved a complete response and one patient a partial response. Dermatitis acneiform, diarrhea, nausea, and vomiting were the most frequently reported adverse events with AZD6244, compared with fatigue, anemia, nausea, anorexia, and dermatitis acneiform with pemetrexed.

Conclusions: Oral AZD6244 showed clinical activity as second- or third-line therapy for patients with advanced NSCLC. In an unselected NSCLC population, there is no suggestion that AZD6244 monotherapy offers any advantage over standard treatment with pemetrexed. Based on preclinical data and recent clinical observations, further development of AZD6244 in NSCLC should focus on BRAF or RAS mutation-positive patients and/or AZD6244-based combination regimens.

Key Words: AZD6244, Non-small cell lung cancer, Phase II, Clinical trial, MEK inhibitor.

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Lung cancer is the leading cause of cancer-related death worldwide, and in the US alone, 219,440 new cases and 159,390 deaths are forecast in 2009 (~28% of all cancer deaths).[1] The 5-year survival rate for all stages combined is just 15%.[2] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung malignancies,[2] and the majority of patients present with advanced, unresectable disease. Median survival time for these patients is less than 1 year using current standard of care platinum-based chemotherapeutic regimens,[3,4] and treatment of advanced disease therefore remains a difficult challenge. The introduction and integration of new targeted therapies into the clinical setting promises a new era in the treatment of NSCLC.

The RAS/RAF/MEK/ERK signaling cascade plays an important role in the regulation of processes such as cell proliferation and survival.[5] Aberrant signaling triggered by mutations within the pathway, frequently within the RAS and RAF oncogenes, may contribute to the malignant progression of many human cancers.[6] In the case of NSCLC, KRAS oncogene mu-

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tations, for example, occur in approximately 25% of cases.[7,8] Mitogen-activated protein kinase kinases 1 and 2 (MEK1/2) are attractive therapeutic targets for cancer treatment because of their key position within the Ras/Raf/MEK/ERK pathway. MEK1/2 are situated downstream of Ras and Raf, and furthermore, the only known substrates of MEK1/2 phosphorylation are the extracellular signal-regulated kinases 1 and 2.

AZD6244 is an orally available, potent, selective, ATP-uncompetitive inhibitor of MEK1/2 and has demonstrated activity in preclinical models in a variety of tumors.[9] A phase I clinical trial has established that AZD6244 is well tolerated with a manageable safety profile and has identified 100 mg twice daily as the most suitable dose for subsequent phase II trials because this dose results in target inhibition.[10] Pemetrexed (Alimta; Eli Lilly and Company, Indianapolis, IN) is approved and widely used for second- or third-line treatment of advanced NSCLC,[11] having demonstrated comparable clinical efficacy and improved safety when compared with docetaxel in patients with NSCLC previously treated with chemotherapy.[12] In this study, we evaluated the efficacy and safety of AZD6244 versus pemetrexed as a second-/third-line treatment in patients with advanced NSCLC.

PATIENTS AND METHODS

Patient Selection

Eligible patients were aged ≥18 years with histologically or cytologically confirmed NSCLC who had previously received one or two chemotherapeutic regimens, had a World Health Organization performance status 0 to 2, and had a life expectancy >12 weeks. Patients were suitable for treatment with pemetrexed and had adequate hepatic (total bilirubin <1.5 × upper limit of normal [ULN] and alanine aminotransferase and aspartate aminotransferase <2.5 × ULN irrespective of whether liver metastases present) and renal (creatinine clearance ≥45 ml/min and serum creatinine <1.25 × ULN) function and adequate bone marrow reserve (platelets ≥100,000/μl, hemoglobin ≥10 g/dl, and absolute neutrophil count ≥1500/μl). Prior surgery and/or local irradiation were allowed, but previous therapy with a MEK inhibitor or pemetrexed was not permitted.

This study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization/Good Clinical Practice. All patients gave written informed consent.

Study Objectives

The primary objective of this study was to evaluate the efficacy of AZD6244 versus pemetrexed in the second- or third-line treatment of advanced NSCLC by assessment of disease progression. The secondary objective of the study was to assess the safety and tolerability of AZD6244 in the treatment of NSCLC by review of adverse events (AEs) and laboratory parameters.

Study Design

This was a phase II, multicenter, open-label, randomized, two-arm, parallel-group study. Patients were randomized in a 1:1 ratio to receive either 100 mg oral AZD6244 free-base suspension twice daily or 500 mg/m^2 pemetrexed by intravenous infusion over 10 minutes every 3 weeks. Patients in the pemetrexed group received premedication with a corticosteroid and vitamin supplementation with folic acid and vitamin B12. Patients were not required to have measurable disease (defined by Response Evaluation Criteria in Solid Tumors [RECIST][13]) at baseline.

AZD6244 dose reductions were permitted, initially to 50 mg twice daily and then to 50 mg once daily. Dose reductions below 50 mg once daily were not allowed, and dose re-escalation was not permitted. Pemetrexed dose reductions were allowed to manage hematologic toxicity as part of routine clinical practice. Patients continued to receive AZD6244 or pemetrexed until objective and/or clinical progression were observed, provided they were deriving clinical benefit, and there was no unacceptable toxicity. At the investigators' discretion, patients who discontinued treatment could proceed with other treatments or participate in other studies.

Assessments

The adopted study design removed, as far as possible, the need for regular tumor assessments of disease status to simplify the study with regard to data collection and frequency of assessments. Therefore, tumor assessments were performed at screening and then per site clinical practice. There was a mandatory tumor assessment for all patients who had not previously progressed at a fixed calendar date ±3 days. A physical examination was given to all patients at screening and then every 3 weeks (±3 days) from week 3 onward. Because tumor response was not an end point of the study, confirmation of response by repeat tumor measurements was not required by the study protocol. Disease progression was assessed using RECIST. Objective progression was defined as ≥20% increase in the sum of longest diameters of measurable lesions, presence of new lesions, or unequivocal progression of nonmeasurable lesions. Lesions in previously irradiated areas were considered evaluable for progression. Clinical disease progression was defined as a global deterioration of health status requiring discontinuation of treatment as a result of the underlying disease and not due to intercurrent illness or adverse effects from therapy. All safety data were based on the event-free survival (EFS) population (all patients who received at least one dose of study medication). Patients were evaluated for AEs throughout the study (at weeks 1–3 and then every 3 weeks while on study treatment until data cutoff) and until 30 days after study drug discontinuation. All AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

Statistical Analyses

The study was designed as a randomized exploratory study to quantify the level of risk entailed for further devel-

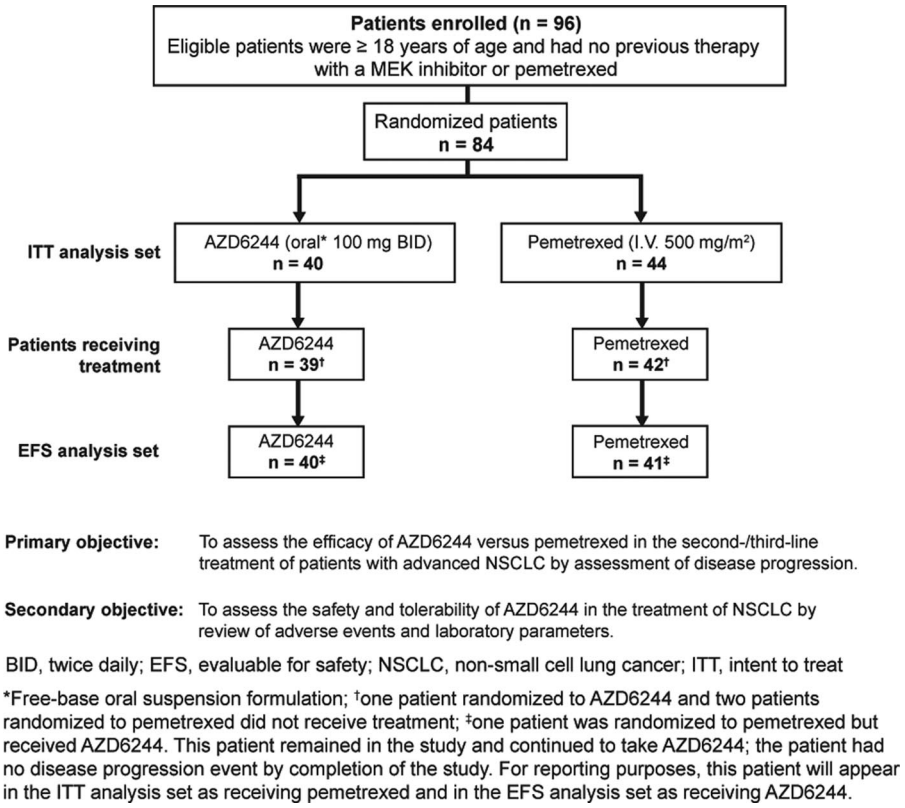

FIGURE 1. AZD6244 versus pemetrexed study design.

opment,[14] and the aim was to identify whether there was a clear signal of activity of AZD6244 in advanced NSCLC. The proportion of patients experiencing a disease progression event on or before the data cutoff point was compared between the treatment arms using a logistic regression model, with a complementary log-log function and including a factor for treatment group. Results were approximated as a hazard ratio (HR) and reported with the corresponding confidence interval (CI) and *p* value. Disease progression event count has been shown to be a good assessment for phase II decision making,[15,16] because it does not rely on time-dependent events that may overestimate progression times and potentially introduce bias when comparing treatments. Analysis of progression event count requires less intensive monitoring of patients and provides an unbiased estimate of the HR. A progression event was defined as the earliest of (i) objective and/or clinical progression on or before the data cutoff point, as measured using RECIST, or (ii) death by any cause. The timing of the analysis (i.e., data cutoff) was guided by the target number of patients with a disease progression event. A total of 38 progression events would ensure that the study had at least 80% power to detect a true HR of 0.50 at the two-sided 20% significance level. As such, a result from this study would be considered statistically significant if the two-sided *p* value was less than 0.2. Therefore, a minimum of 64 patients were required and the data cutoff was set when approximately 60% of patients had experienced disease progression events. The analysis was performed on an intent to treat (ITT) basis using the ITT analysis set (all randomized patients), and patients were analyzed according to their randomized study drug. Taking into account the timing of a progression event (as assessed by the investigator), an exploratory analysis was also performed in support of the progression-event count analysis. This analysis and the investigator's assessed best response were not robust, because the protocol did not require regular tumor assessments or patients to have measurable disease at baseline.

RESULTS

Demographic and Baseline Characteristics

Eighty-four patients from 10 centers (4 in the US, 4 in Bulgaria, and 2 in Romania) were randomized to study treatment (40 and 44 patients in the AZD6244 and pemetrexed treatment groups, respectively; Figure 1), and these comprised the ITT population. Both treatment groups were generally comparable with respect to demographic and baseline characteristics (Table 1).

Efficacy

In the ITT analysis set, 28 (70%) patients in the AZD6244 group compared with 26 (59%) patients in the pemetrexed group had a disease progression event. The resulting HR was 1.35, and this difference was not statistically significantly different as $p > 0.2$ (two-sided 80% CI = 0.93–1.94; two-sided 95% CI = 0.77–2.36; $p = 0.30$).

There was no significant difference between the two treatment groups in terms of progression-free survival (PFS)

TABLE 1. Demographic Characteristics (ITT Population)

Characteristics	Patients, *n* (%) AZD6244 (*n* = 40)	Pemetrexed (*n* = 44)
Age (yr)		
Mean (SD)	59.2 (12.58)	62.7 (8.35)
Median (range)	61.5 (21–79)	63.5 (43–80)
Sex		
Male	26 (65)	27 (61)
Female	14 (35)	17 (39)
Race		
Caucasian	39 (98)	42 (95)
Black	1 (3)	1 (2)
Other	0	1 (2)
Region		
Europe	24 (60)	28 (64)
USA	16 (40)	16 (36)
Number of previous therapies		
One	31 (78)	35 (80)
Two	9 (23)	9 (20)
Previous treatments		
High-dose radiation[a]	13 (33)	18 (41)
Platinum therapy	37 (93)	42 (95)
Taxane therapy	18 (45)	21 (48)
EGFR inhibitor therapy	1 (3)	1 (2)
Responded to EGFR inhibitor therapy	1 (3)	1 (2)
Diagnosis of adenocarcinoma	15 (38)	20 (45)
Time since diagnosis of advanced disease		
<1 yr	29 (73)	35 (80)
≥1 yr	11 (28)	9 (20)
Smoking status[b]		
Nonsmoker	6 (15)	12 (27)
Ex-smoker	18 (45)	18 (41)
Occasional smoker	0	0
Habitual smoker	16 (40)	14 (32)
Pack-years[c]		
Mean (SD)	30.1 (22.50)	25.6 (20.99)
Median (range)	30.0 (0–99)	26.5 (0–75)

[a] High-dose radiation was defined as >60 Gy.
[b] Smoking status was defined as nonsmoker (never smoked), ex-smoker (no cigarettes smoked in last 6 mo), occasional smoker (<1 cigarette per day), or habitual smoker (>1 cigarette per day).
[c] A pack-year was defined as 20 cigarettes/d/yr.
EGFR, epidermal growth factor receptor.

in the ITT population (Figure 2). Median PFS in the ITT analysis set was 90 days in the pemetrexed treatment arm compared with 67 days in the AZD6244 group (HR = 1.08; two-sided 80% CI = 0.75–1.54; two-sided 95% CI = 0.62–1.86; $p = 0.79$). The majority of patients were treated until progression. Given that the protocol did not require regular tumor assessments, it is possible that the time to progression may have been overestimated for some patients.

In total, four patients (two in each treatment group) in both the ITT and EFS populations achieved a best overall response according to RECIST of complete or partial response at the time of the mandatory tumor assessment (Table 2). In the pemetrexed group, one patient had a complete response and one had a partial response (total treatment duration of 53 days for both patients). In the AZD6244 group, two patients achieved a partial response with total treatment durations of 76 and 78 days, respectively. All the four patients were still receiving treatment at the time of the mandatory tumor assessment. However, the protocol did not require regular tumor assessments; therefore, an interim scan may potentially have identified patients who had a better tumor response than that reported here. Furthermore, patients were not required to have measurable disease at baseline.

Safety

Median actual exposure to AZD6244 and pemetrexed was 63 and 61 days, respectively, at the time of data cutoff. Treatment was discontinued in the majority of patients before data cutoff (75% and 61% in the AZD6244 and pemetrexed treatment groups, respectively), primarily as a result of disease progression. Ten (25%) patients in the AZD6244 group and eight (20%) patients in the pemetrexed group experienced AEs that led to dose reduction, dose interruption, or treatment discontinuation.

The majority of patients in both treatment groups experienced ≥1 AE causally related to treatment (28 [70%] patients and 29 [71%] patients in the AZD6244 and pemetrexed groups, respectively), and the majority were of mild to moderate severity. The most common treatment-related AEs reported in the AZD6244 group were dermatitis acneiform and diarrhea (Table 3). The most frequently observed treatment-related AEs with pemetrexed were fatigue, anemia, and nausea.

Treatment-related serious adverse events were experienced by three patients in the pemetrexed group (secondary myelodysplastic syndrome in one patient and neutropenia in two patients [one patient had two serious adverse events of neutropenia]) and by one patient in the AZD6244 group (respiratory failure, resulting in patient death).

A total of 8 (20%) deaths were recorded in each treatment group before study termination (30 days after the last dose of study treatment for an individual patient), the majority of which were the result of disease progression or AEs related to NSCLC that could be expected in a population with advanced NSCLC and its associated comorbidities. One patient in the pemetrexed treatment group died because of an AE of myocardial infarction. The fatal AE of respiratory failure in the AZD6244 group was considered by the investigator to be potentially related to AZD6244 study treatment. This patient was a 33-year-old female nonsmoker diagnosed with adenocarcinoma. Onset of constant CTCAE grade 3 dyspnoea that was considered possibly related to AZD6244 treatment occurred 6 days after starting the treatment. The event of dyspnoea worsened to CTCAE grade 4 that day, and treatment was permanently discontinued. The patient's condition continued to deteriorate, resulting in hospitalization on day 18, and she died of respiratory failure after 24 days. The investigator considered disease progression to be the likely cause of death; however, a computed tomography scan

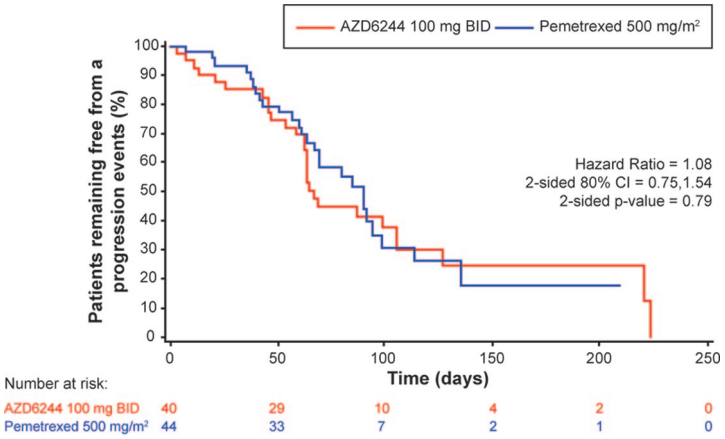

FIGURE 2. Comparison between AZD6244 and pemetrexed in terms of progression-free survival (ITT [intent to treat] population).

performed after admission to hospital did not show clear evidence of disease progression. As a result, the investigator could not eliminate the possibility that the respiratory failure was causally related to treatment with AZD6244.

Laboratory and Clinical Parameters

Both AZD6244 and pemetrexed were associated with small mean increases in alanine aminotransferase and aspartate aminotransferase within normal ranges. Treatment with AZD6244 was associated with fewer clinically relevant changes in hematology variables compared with pemetrexed. Sixteen (43%) patients who received AZD6244 experienced CTCAE grade 1–2 decrease in hemoglobin level, compared with 25 (63%) patients in the pemetrexed group with CTCAE grades 1 to 4. Decrease in white blood cells, neutrophils, and platelets count was experienced by 3% ($n = 1$), 5% ($n = 2$), and 3% ($n = 1$) of patients in the AZD6244 group, compared with 53% ($n = 21$), 48% ($n = 19$), and 23% ($n = 9$) of patients in the pemetrexed group. Overall, no new safety concerns for AZD6244 were identified from the hematology and clinical chemistry results.

DISCUSSION

In this phase II signal searching study in a broad population of pretreated patients with advanced NSCLC, AZD6244 did not demonstrate superiority to pemetrexed in terms of efficacy. However, no significant differences between the two treatment arms were observed in terms of the proportion of patients with

TABLE 2. Investigators' Assessment of Best Overall Response in Accordance with RECIST (ITT Population)[a]

Randomized Treatment	*n*	Patients, *n* (%)				
		Complete Response	Partial Response	Stable Disease	Progressive Disease	Not Evaluable
AZD6244	40	0	2 (5)	14 (35)	18 (45)	6 (15)[b]
Pemetrexed	44	1 (2)	1 (2)	21 (48)	18 (41)	3 (7)[c]

[a] Given that the protocol did not require regular tumor assessments, it is possible that an interim scan may have identified patients who had a better tumor response than that reported here. In addition, patients were not required to have measurable disease at baseline.

[b] One patient had rapid progression and died 4 d after the start of the study. A second patient received no study treatment; time to progression was 4 d with subsequent death. A third patient had a prolonged QTc interval at screening; the patient stopped treatment after 1 wk of AZD6244 (progression occurred 219 d after randomization). A fourth patient progressed and died due to respiratory failure 25 d after randomization. A fifth patient withdrew their consent, and a sixth patient had rapid progression and subsequently died 8 d after randomization.

[c] One patient died 63 d after randomization from a myocardial infarction before the follow-up scan. A second patient did not receive study treatment; their time to progression was 57 d and they died 146 d after randomization. A third patient withdrew their consent.

TABLE 3. Number of Patients with the Most Frequently Reported (≥10% of All Patients) Treatment-Related Adverse Events (EFS Population)

Preferred Term	Patients, *n* (%)	
	AZD6244 (*n* = 40)	Pemetrexed (*n* = 41)
Nonhematologic adverse events		
Dermatitis acneiform	17 (43)	7 (17)
Diarrhea	12 (30)	2 (5)
Nausea	7 (18)	9 (22)
Vomiting	7 (18)	7 (17)
Fatigue	5 (13)	15 (37)
Anorexia	3 (8)	6 (15)
Hematologic adverse events		
Anemia	2 (5)	12 (29)
Neutropenia[a]	0	7 (17)

[a] As per the study protocol, abnormalities in the laboratory findings were only to be reported as adverse events if they fulfilled any criterion for a serious adverse event, if the laboratory abnormalities caused the patient to discontinue from the study, or if the investigator insisted that the abnormality should be reported as an adverse event. Therefore, the number of reported adverse events of neutropenia may not match the results derived from the laboratory findings.

a disease progression event (59% versus 70%, respectively; HR = 1.35; two-sided 80% CI = 0.93–1.94; two-sided 95% CI = 0.77–2.36; $p = 0.30$) and PFS (HR = 1.08; two-sided 80% CI = 0.75–1.54; two-sided 95% CI = 0.62–1.86; $p = 0.79$). Response rates were also similar in patients receiving either AZD6244 or pemetrexed (5.0% versus 4.5%, respectively). Confidence intervals were typically wide for comparison of the efficacy analyses in this study in light of the small patient numbers. Furthermore, it should be noted that the PFS and tumor response data were not robust because the protocol did not require regular tumor assessments, and patients were not required to have measurable disease at baseline.

The efficacy of pemetrexed observed in this study was consistent with previous experience with pemetrexed in the second- and third-line treatment of advanced NSCLC.[12,17,18] Response rates for 3-weekly 500 mg/m^2 pemetrexed in previous studies were slightly higher than that in this study, ranging from 7.1 to 11.2%. Median PFS was 90 days in this study, compared with 2.6 months in the study by Cullen et al.,[18] 2.9 months in the study by Hanna et al.,[12] and 3.0 months in the study by Bearz et al.[17]

Of note, a number of recent studies have shown that tumor histology impacts on the efficacy of pemetrexed, with better efficacy reported in patients with nonsquamous tumors than in those with squamous cell carcinomas.[19–21] A retrospective analysis of the study by Hanna et al.,[12,21] for example, found that pemetrexed efficacy varied between squamous and nonsquamous histologic subtypes in terms of overall survival (6.2 versus 9.3 months), PFS (2.3 versus 3.1 months), and tumor response rates (2.8% versus 11.5%). Accordingly, the second-line indication for pemetrexed was revised in 2008 to include only patients with nonsquamous advanced or metastatic NSCLC.[22] This study, which began before the pemetrexed label change, did not exclude patients with squamous histology and did not stratify patients by histologic status; therefore, the activity of pemetrexed in the nonsquamous population for which the drug is currently indicated may be underestimated.

As with pemetrexed, it has been suggested that sensitivity to AZD6244 may also be higher in certain patient subgroups. A recent in vitro study demonstrated a tendency toward sensitivity to AZD6244 in cell lines harboring BRAF or RAS gene mutations compared with those with wild-type genes.[23] A similar observation was reported in a recent phase II study comparing AZD6244 with temozolomide in patients with advanced or metastatic melanoma in which five of six (83%) patients who achieved confirmed partial responses with AZD6244 had BRAF mutation-positive tumors.[24] It was unknown at the start of this study which mutations may confer sensitivity to AZD6244, and therefore, a broad population of patients was assessed.

AZD6244 was generally well tolerated, which was reflected by the low number of dose reductions or treatment interruptions. Most patients in both treatment arms experienced at least one AE, and the number and types of AEs were consistent with the nature of the study treatments and the disease under study. The AE profile varied between the treatment groups. AZD6244 was associated with more dermatitis acneiform and diarrhea than pemetrexed, which is consistent with the previously reported safety profile for AZD6244.[10] Fatigue, anemia, neutropenia, and anorexia were more commonly associated with pemetrexed than AZD6244, which is also comparable with the safety profile for pemetrexed reported in the literature.[12,17,18] Consistent with its AE profile in this study, pemetrexed was also associated with greater and more serious decreases in hemoglobin levels than AZD6244, as well as greater decreases in the number of white blood cells, neutrophils, and platelets.

CTCAE grade 3 or higher AEs were experienced by a similar number of patients in both treatment groups, although CTCAE grade 4 AEs were more prevalent in the pemetrexed arm of the study. The rates of CTCAE grade 3/4 neutropenia and anemia observed with pemetrexed in this study (10% and 10%, respectively) were higher than those reported in the studies by Hanna et al., Bearz et al., and Cullen et al.,[12,17,18] which reported grade 3/4 neutropenia in 5.3%, 1.9%, and 2.1% of patients and grade 3/4 anemia in 4.2%, 1.9%, and 1.4% of patients, respectively. Serious adverse events were experienced by more patients in the pemetrexed arm of this study than in the AZD6244 arm (17% versus 10%, respectively), although in both treatment groups, SAEs were indicative of a population with advanced NSCLC. Overall, the safety and laboratory results of this study did not indicate any new safety concerns for AZD6244.

In conclusion, the results of this study showed that the oral MEK1/2 inhibitor AZD6244 is a well-tolerated treatment regimen, with clinical activity as a second- or third-line treatment in a broad population of patients with advanced NSCLC. As a single agent, there was no indication of superiority to standard treatment with pemetrexed in this randomized phase II study. Further development of AZD6244 in NSCLC should focus on patients with demonstrated mutations of the BRAF or RAS oncogenes or on the development of rational combination regimens.

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REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225–249.
2. American Cancer Society. Cancer facts & figures 2009. Available at: http://www.cancer.org/downloads/STT/500809web.pdf. Accessed June 25, 2009.
3. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003;21:3016–3024.
4. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemother-

apy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–3551.
5. Wang D, Boerner SA, Winkler JD, et al. Clinical experience of MEK inhibitors in cancer therapy. *Biochim Biophys Acta* 2007;1773:1248–1255.
6. Zebisch A, Czernilofsky AP, Keri G, et al. Signaling through RAS-RAF-MEK-ERK: from basics to bedside. *Curr Med Chem* 2007;14:601–623.
7. Huncharek M, Muscat J, Geschwind JF. K-ras oncogene mutation as a prognostic marker in non-small cell lung cancer: a combined analysis of 881 cases. *Carcinogenesis* 1999;20:1507–1510.
8. Schiller JH, Adak S, Feins RH, et al. Lack of prognostic significance of p53 and K-ras mutations in primary resected non-small-cell lung cancer on E4592: a Laboratory Ancillary Study on an Eastern Cooperative Oncology Group Prospective Randomized Trial of Postoperative Adjuvant Therapy. *J Clin Oncol* 2001;19:448–457.
9. Yeh TC, Marsh V, Bernat BA, et al. Biological characterization of ARRY-142886 (AZD6244), a potent, highly selective mitogen-activated protein kinase kinase 1/2 inhibitor. *Clin Cancer Res* 2007;13:1576–1583.
10. Adjei AA, Cohen RB, Franklin W, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. *J Clin Oncol* 2008;26:2139–2146.
11. NCCN Practice Guidelines in Oncology™. Non-small cell lung cancer (version 2.2009). Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed June 25, 2009.
12. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589–1597.
13. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
14. Rubinstein LV, Korn EL, Freidlin B, et al. Design issues of randomized phase II trials and a proposal for phase II screening trials. *J Clin Oncol* 2005;23:7199–7206.
15. Stone A, Wheeler C, Carroll K, et al. Optimizing randomized phase II trials assessing tumor progression. *Contemp Clin Trials* 2007;28:146–152.
16. Carroll KJ. Analysis of progression-free survival in oncology trials: some common statistical issues. *Pharm Stat* 2007;6:99–113.
17. Bearz A, Garassino I, Cavina R, et al. Pemetrexed single agent in previously treated non-small cell lung cancer: a multi-institutional observational study. *Lung Cancer* 2008;60:240–245.
18. Cullen MH, Zatloukal P, Sorenson S, et al. A randomized phase III trial comparing standard and high-dose pemetrexed as second-line treatment in patients with locally advanced or metastatic non-small-cell lung cancer. *Ann Oncol* 2008;19:939–945.
19. Okabe T, Kubota K, Tamura T, et al. Prognostic factors affecting survival on pretreated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)—subgroup analysis in a randomized Ph II study of pemetrexed 500 mg/m^2 and 1000 mg/m^2. *Eur J Cancer Suppl* 2007;5:376.
20. Peterson P, Park K, Fossella F, et al. Is pemetrexed more effective in adenocarcinoma and large cell lung cancer than in squamous cell carcinoma? A retrospective analysis of a phase III trial of pemetrexed vs docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2007;2:S851.
21. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. *Oncologist* 2009;14:253–263.
22. ALIMTA® prescribing information. Eli Lilly and Company. Available at: http://pi.lilly.com/us/alimta-pi.pdf. Accessed August 6, 2009.
23. Davies BR, Logie A, McKay JS, et al. AZD6244 (ARRY-142886), a potent inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1/2 kinases: mechanism of action in vivo, pharmacokinetic/pharmacodynamic relationship, and potential for combination in preclinical models. *Mol Cancer Ther* 2007;6:2209–2219.
24. Dummer R, Robert C, Chapman PB, et al. AZD6244 (ARRY-142886) vs temozolomide (TMZ) in patients (pts) with advanced melanoma: an open-label, randomized, multi-center, phase II study. *J Clin Oncol* 2008;26:Abstract 9033.