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ORIGINAL ARTICLE

A Phase I study to assess the safety, tolerability, and pharmacokinetics of AZD4877, an intravenous Eg5 inhibitor in patients with advanced solid tumors

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Abstract
Purpose Inhibition of kinesin spindle protein or Eg5 causes the formation of monoastral mitotic spindles, which leads to cell death. AZD4877 is a specific, potent inhibitor of Eg5.
Methods This was a Phase I, open-label, two-part study to evaluate the maximum tolerated dose (MTD) and safety and tolerability of AZD4877 in patients with advanced solid malignancies. In part A, the MTD of AZD4877, administered as three weekly 1-h intravenous (iv) infusions in a 28-day schedule, was determined by evaluating dose-limiting toxicity (DLT). In part B, the safety, tolerability, and pharmacokinetic profile of AZD4877 at the MTD were evaluated.
Results In part A, 29 patients received at least one dose of AZD4877 (5 mg, $n = 4$; 7.5 mg, $n = 4$; 10 mg, $n = 3$; 15 mg, $n = 3$; 20 mg, $n = 3$; 30 mg, $n = 6$; 36 mg, $n = 3$; 45 mg, $n = 3$). The MTD was defined as 30 mg, with the primary DLT being neutropenia. Although exposures appeared to be similar at the AZD4877 20 and 30 mg doses, dose reductions and omissions were higher in the 30-mg cohort; therefore, an intermediate dose, 25 mg, was evaluated in part B ($n = 14$). In part B, neutropenia remained the most commonly reported causally related adverse event. Exposure to AZD4877 was approximately dose proportional. Severity of neutropenia was related to exposure.
Conclusion The MTD of AZD4877 given as a 1-h iv infusion on days 1, 8, and 15 of a 28-day cycle was 30 mg. At the selected 25 mg dose, AZD4877 had an acceptable safety profile.

Keywords AZD4877 · Eg5 · Solid tumors · Safety · Tolerability · Pharmacokinetics

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Introduction

During mitosis, replicated DNA is segregated into two daughter cells by the action of the mitotic spindle. The spindle is formed primarily of microtubules arranged into two bipolar arrays by the action of motor and microtubule-associated proteins [1]. In the event that a functional spindle does not form, normal chromosomal segregation is not achieved and checkpoint proteins prevent cell division from occurring, leading to mitotic arrest [2].

Kinesin spindle protein, also known as Eg5, is a motor protein essential for mitotic spindle formation and normal

chromosome separation during mitosis [3]. Increased expression of Eg5, and a number of other mitosis-associated markers, is observed in human proliferative tissues including thymus, tonsil, testis, esophageal epithelium, and bone marrow. In addition, Eg5 is overexpressed in solid tumors and leukemias, supporting a rationale for targeting Eg5 as an approach to cancer therapy [4–6].

Inhibition of Eg5 in replicating cells has been shown to prevent centrosomal separation and mitotic spindle assembly. This leads to the formation of monopolar spindles ("monoasters"), activation of spindle checkpoint proteins, and mitotic arrest, which eventually brings about cell death [3, 7, 8]. Notably, inhibition of Eg5 has been shown to cause cell death in a number of experimental cancer cell lines and to have antitumor activity in human xenograft models [9–13].

Inhibition of Eg5 affects only cells actively in mitosis and has no detectable effect on the microtubular architecture [14]. Unlike traditional antimitotic agents such as the taxanes and vinca alkaloids, which target the microtubules and affect cell functions beyond mitosis, Eg5 inhibition is not expected to affect non-proliferating cells [15]. Furthermore, Eg5 is not expressed in the adult peripheral nervous system; therefore, Eg5 inhibitors are not expected to cause neuropathic side effects that are commonly associated with agents that primarily target tubulin [4, 13].

AZD4877 is a specific and potent inhibitor of Eg5 that has been shown to prevent centrosome separation and mitotic spindle assembly, leading to mitotic arrest and cell death in preclinical models [16]. In vitro, AZD4877 has shown activity across a broad range of solid tumor and hematologic cell lines. Preclinical toxicology studies have shown that AZD4877 has a dose-related and reversible effect on the bone marrow, gastrointestinal tract, and other proliferating tissues (data on file).

The primary objectives of this Phase I study were to identify the maximum tolerated dose (MTD) of AZD4877 based on the assessment of dose-limiting toxicity (DLT) and to evaluate the pharmacokinetic (PK) parameters of AZD4877 when administered as three successive weekly 1-h intravenous (iv) infusions on days 1, 8, and 15 of a 28-day cycle (3 weeks on then 1 week off). The safety, tolerability, and efficacy of AZD4877 were also assessed.

Methods

Patients

Patients aged ≥18 years were eligible for inclusion in the study if they had a metastatic or unresectable solid malignancy, without marrow involvement (including non-Hodgkin lymphoma), for which standard curative or palliative measures either did not exist or were no longer effective. Patients were required to have a World Health Organization (WHO) performance status of 0 or 1 and be likely to complete 4 weeks of therapy and observation. Patients who had received an investigational or standard anticancer agent or radiotherapy within 14 days of the first dose of study treatment were excluded from the study. Other exclusion criteria included inadequate bone marrow reserve as demonstrated by absolute neutrophil count (ANC) $<1.5 \times 10^9$/l, platelet count $<100 \times 10^9$/l or hemoglobin ≤9 g/l, or inadequate renal or liver function as well as evidence of severe or uncontrolled systemic disease.

All patients provided written informed consent. The study was approved by the independent ethics committee for each trial center and was conducted in accordance with the Declaration of Helsinki [17].

Study design

This was an open-label, two-part, Phase I study (Clinicaltrials.gov identifier NCT00389389). In part A, the MTD of AZD4877 was evaluated in cohorts of at least three evaluable patients. An evaluable patient was any patient who had either completed cycle 1 or experienced a DLT during cycle 1. AZD4877 was administered in a range of escalating doses of 5, 7.5, 10, 15, 20, 30, 36, and 45 mg as a 1-h iv infusion on days 1, 8, and 15 of a 28-day cycle. Based on evaluation of the MTD defined in part A, a dose was selected for the evaluation in at least 12 patients in part B, the dose-expansion part of the study. Following the completion of cycle 1 in both parts A and B, individual patients could receive continued treatment with AZD4877 if they continued to benefit and there was no evidence of disease progression.

The primary objectives were to identify the MTD of AZD4877 based on the assessment of DLTs and to determine the PK profile of AZD4877 for the weekly schedule based on the following PK parameters obtained during cycle 1: maximum plasma drug concentration after single dose administration (C_{max}); area under the plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$); and plasma drug concentration at 24 h after administration of a given dose ($C_{24\ h}$).

Secondary objectives included evaluation of the safety and tolerability of AZD4877, and determination of additional PK parameters of AZD4877 for the weekly schedule, obtained during cycle 1 including: area under the plasma concentration–time curve from zero to 24 h (AUC_{0-24}); total body clearance of drug from plasma (CL); half-life associated with the terminal slope of a semilogarithmic concentration–time curve ($t_{1/2}$); mean residence time (MRT); and volume of distribution at steady state (V_{ss}). Exploratory objectives included evaluation of the relationship between

the incidence of neutropenia and plasma exposure to AZD4877, by evaluation of appropriate PK and hematology parameters, and assessment of the antitumor activity of AZD4877.

Assessments

The MTD was defined as the highest dose at which no more than one of six evaluable patients experienced a DLT during cycle 1. The definition of a DLT included grade 4 neutropenia >4 days, grade 4 thrombocytopenia, grade 3 neutropenia with fever, and any grade 3 non-hematological toxicity. Dose modifications (25 or 50% reductions) were allowed within a treatment cycle and at the beginning of subsequent cycles, depending on the severity of neutropenia or non-hematological toxicities. Granulocyte colony-stimulating factor (G-CSF) use was not permitted during cycle 1, except in concordance with American Society of Clinical Oncology guidelines [18]. In part B, AZD4877 was administered at a weekly dose of 25 mg as a 1-h iv infusion, selected on the basis of tolerability. Safety was evaluated by the assessment of adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The incidence of DLTs during cycle 1, AEs, and serious AEs are reported.

Venous blood samples for PK analysis were taken pre-dose, at 30 and 55 min after the start of infusion and at 5, 15 and 30 min, and 1, 2, 4, 6–8, 24, 26 and 46–48 h after the end of infusion on cycle 1, day 1. During cycle 2, samples were taken pre-dose and 55 min after the start of infusion.

Pharmacodynamic (PD) assessment consisted of measurement of the percentage change from baseline in ANC during cycle 1 and assessment of the presence of monoasters in peripheral blood mononuclear cells (PBMCs) as an indicator of Eg5 inhibition. The presence of monoasters in PBMCs was assessed pre-dose, 6–8, and 24 h after the first infusion of AZD4877. PBMCs were prepared from whole blood using cell preparation tubes (Becton–Dickinson, Franklin Lakes, NJ, USA), washed in phosphate-buffered saline, centrifuged onto glass slides, and air-dried. Immunohistochemical staining for α-tubulin was performed on the Ventana Discovery XT system slide stainer using the OmniMap detection kit (Ventana, Tucson, AZ, USA) according to the manufacturer's instructions. Total cell counts were determined by image analysis using Aperio IHC Nuclear Algorithm software (Aperio Technologies Inc. Vista, CA, USA), and monoasters were scored manually. Monoaster counts were expressed as number per 10,000 PBMCs with a mean of 100,000 cells counted for each assessment.

Overall best response and the number of patients with stable disease (SD) >12 weeks were assessed by study investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [19].

Statistical analysis

Descriptive statistics was used to summarize safety, tumor assessment, and PK parameters from all dosed patients. The relationship between the maximum percentage decrease in ANC and exposure to AZD4877 ($C_{24\ h}$, C_{max} and $AUC_{0-\infty}$) was analyzed according to an E_{max} model or sigmoid E_{max} model for the exposure $C_{24\ h}$, C_{max}, and $AUC_{0-\infty}$.

Results

Patients

A total of 51 patients consented to enroll in this study, 43 of whom received at least one dose of AZD4877 (29 in part A and 14 in part B; Table 1). Mean age was 61.2 years (range 39–83), 36 patients (84%) were Caucasian, and 27 (63%) were men. All patients had metastatic disease with a broad representation of primary tumor types, of which colon/colorectal/rectal (23%), bladder (12%), and pancreatic (12%) cancers were the most commonly reported. Of the 43 patients who received at least one dose of AZD4877, all discontinued from the study; the most common reason for discontinuation was lack of therapeutic response (84%).

Of the 29 patients who received treatment in part A, three were considered non-evaluable for DLTs, either because treatment was discontinued prior to the completion of cycle 1 before a DLT had occurred, or because assessment of DLTs was not possible due to protocol deviations. Furthermore, two patients in part B were considered non-evaluable for efficacy, as they did not have any follow-up RECIST assessment due to early discontinuation from the study.

The median duration of treatment across all AZD4877 dose groups was 43 days (range 1–316), with the longest median duration being in the 45-mg dose cohort. The median number of treatment cycles initiated across all the dose ranges was two (range 1–12). All three patients in the 45-mg dose cohort who had median treatment durations of 22, 101, and 316 days had their doses reduced or omitted by cycle 2.

Safety

The DLTs reported during part A of the study are shown in Table 2. No DLTs were reported in the patient cohorts receiving AZD4877 ≤20 mg. The 30-mg cohort was

Table 1 Baseline demographic characteristics

	Part A ($n = 29$)	Part B ($n = 14$)	Total ($n = 43$)
Age, years			
Mean (standard deviation)	58.8 (11.6)	66.0 (12.1)	61.2 (12)
Range	39–82	43–83	39–83
Gender, *n* (%)			
Male	18 (62)	9 (64)	27 (63)
Female	11 (38)	5 (36)	16 (37)
Race, *n* (%)			
White	24 (83)	12 (86)	36 (84)
Black African/American	4 (14)	2 (14)	6 (14)
Asian	1 (3)	0	1 (2)
Prior radiotherapy, *n* (%)	16 (55)	11 (79)	27 (63)
Prior chemotherapy regimens			
Median	4	3	4
Range	2–10	1–10	1–10
Primary tumor, *n* (%)			
Colon/colorectal/rectal*	9 (31)	2 (14)	11 (25)
Bladder	3 (10)	2 (14)	5 (12)
Pancreas	2 (7)	3 (21)	5 (12)
Lung	1 (3)	2 (14)	3 (7)
Head and neck	1 (3)	1 (7)	2 (5)
Esophagus	1 (3)	1 (7)	2 (5)
Prostate	2 (7)	0	2 (5)
Gastroesophageal junction	2 (7)	0	2 (5)
Skin/soft tissue	1 (3)	1 (7)	2 (5)
Other†	7 (24)	2 (21)	9 (21)

* Also includes small bowel and appendix. † Other includes one each of biliary tract, lymph nodes, fallopian tube, thymus, pleural/pleural effusion (mesothelioma), renal, and thyroid in Part A, and one each of melanoma and stomach in Part B

Table 2 Dose-limiting toxicities observed in patients evaluable for DLT in part A

AZD4877 dose (mg)	Number of patients experiencing DLTs/number of dosed patients evaluable for DLT in the cohort	DLTs (CTCAE grade)
5	0/3	None
7.5	0/3	None
10	0/3	None
15	0/3	None
20	0/3	None
30	1/6	Neutropenia (grade 4) and pulmonary embolism (grade 4) in one patient
36*	3/3	Neutropenia (grade 4) in two patients
		Neutropenia (grade 4), mucosal inflammation (grade 3), and febrile neutropenia (grade 3) in one patient
45	2/2	Neutropenia (grade 4) in two patients

DLT dose-limiting toxicity

CTCAE Common Terminology Criteria for Adverse Events, version 3.0

* Intermediate dose

expanded to six patients due to one patient experiencing DLTs of grade 4 neutropenia and grade 4 pulmonary embolism. Furthermore, the first two patients recruited into the 45-mg dose cohort also experienced DLTs of grade 4 neutropenia. Consequently, an intermediate dose of 36 mg was evaluated. However, this dose was declared intolerable due to DLTs of neutropenia (grade 4), febrile neutropenia (grade 3), and mucosal inflammation (grade 3). Therefore,

the MTD of AZD4877 dosed on days 1, 8, and 15 of a 28-day cycle was defined as 30 mg.

The protocol allowed for flexibility in the selection of the dose to be explored in the dose-expansion phase (part B). In part A, of the six patients in the AZD4877 30-mg cohort, only two received all three infusions in cycle 1. Furthermore, of 18 possible study drug infusions, nine were omitted or reduced in this 30-mg dose group. Conversely, in the 20-mg dose group, there were no dose omissions or reductions. Therefore, the 25 mg dose was selected for evaluation in part B.

The AEs occurring in ≥10% of patients in parts A and B are shown in Table 3. Neutropenia was the most commonly reported CTCAE grade ≥3 event, both during cycle 1 and throughout the study (overall, $n = 9$ [21%]). The median duration of neutropenia from starting AZD4877 treatment was 8 days (range 8–15 days) and was reversible. Febrile neutropenia only occurred in two patients (one in the 36-mg cohort and one in part B, 25 mg). Also, Grade 3 anemia only occurred in two patients (one patient each in the 36- and 45-mg cohorts), and hemolysis was not observed. Thrombocytopenia was reported in two patients (one grade 3 in the 45-mg cohort and one grade 1 in part B). The majority of non-hematological AEs were grades 1 or 2 in severity, with only two patients each with grade 3 constipation, grade 3 abdominal pain, or grade 3 fatigue. There was no increase in preexisting neuropathy and no new neuropathy.

Table 3 Adverse events by grade occurring in ≥10% of patients overall by grade

Patients with AEs, *n* (%)	Maximum CTCAE grade*		
	1 or 2	3	4
Neutropenia	5 (11.6)	9 (20.9)	11 (25.6)
Fatigue	17 (39.5)	2 (4.7)	0
Nausea	15 (34.9)	0	0
Constipation	11 (25.6)	2 (4.7)	0
Vomiting	9 (20.9)	0	0
Abdominal pain	8 (18.6)	2 (4.7)	0
Anorexia	8 (18.6)	0	0
Dyspnea	8 (18.6)	0	0
Diarrhea	7 (16.3)	1 (2.3)	0
Pyrexia	7 (16.3)	0	0
Back pain	6 (14.0)	0	0
Dehydration	6 (14.0)	0	0
Headache	6 (14.0)	0	0
Arthralgia	5 (11.6)	0	0
Pain in extremity	5 (11.6)	0	0

* Each patient is represented once at maximum CTCAE grade for each preferred term

In part B of the study, neutropenia was also the most commonly reported CTCAE grade ≥3 event, occurring in eight patients dosed with AZD4877 25 mg. There were no grade 3 non-hematologic toxicities. The most commonly reported serious AEs were neutropenia (11 of 43 patients) and constipation (three of 43 patients). Four patients discontinued AZD4877 treatment due to AEs (grade 2 partial bowel obstruction, grade 3 constipation, grade 5 acute myocardial infarction (MI), and grade 2 compression fracture), but none of these AEs were considered by the investigator to be treatment related. Three patients experienced AEs that would have fulfilled the criteria for a DLT in part A. Of these, two patients had CTCAE grade 4 neutropenia and one patient died due to an acute MI. Of the 42 possible study drug infusions in part B, 13 (31%) were reduced or omitted during cycle 1 and 32 (76%) were reduced or omitted during cycle 2. All study drug infusions were reduced or omitted by cycle 3. There were four deaths during the study, of which three were due to disease progression and one was due to an acute MI; none of these events were considered by the investigator to be treatment related. The patient who died of an acute MI was a man aged 65 years with a primary small bowel tumor. He died on day 4 after receiving one dose of AZD4877 25 mg on day 1. The patient had a history of coronary artery disease with stent placement, type 2 diabetes, hypertension, hyperlipidemia, abdominal aortic aneurism, and smoking.

Pharmacokinetics

Systemic exposure to AZD4877 increased in an approximately dose-proportional manner (Fig. 1). Following the peak, the plasma concentration of AZD4877 declined in a bi-exponential manner. Total CL was similar across the AZD4877 dose range, and $t_{1/2}$ was approximately 16 h, ranging from 9 to 21 h across the doses. Notably, the 20, 25, and 30 mg doses had similar exposure profiles (Table 4). PK data obtained on day 1 of cycle 2 were similar to those from the initial infusion on day 1 of cycle 1.

Pharmacodynamics

The severity of neutropenia was shown to be correlated with increasing AZD4877 exposure. The relationship between the maximum percentage decrease in ANC and exposure to AZD4877 was best described by a sigmoid E_{max} relationship for the exposure $C_{24\ h}$. As shown in Fig. 2, the severity of neutropenia increased with increasing 24-h plasma concentrations of AZD4877.

Monoaster formation in PBMCs was observed in at least one patient at each of the following doses: 7.5 mg ($n = 1$), 10 mg ($n = 1$), 20 mg ($n = 1$), 25 mg ($n = 1$), 30 mg ($n = 1$), 36 mg ($n = 1$), and 45 mg ($n = 3$), where "*n*"

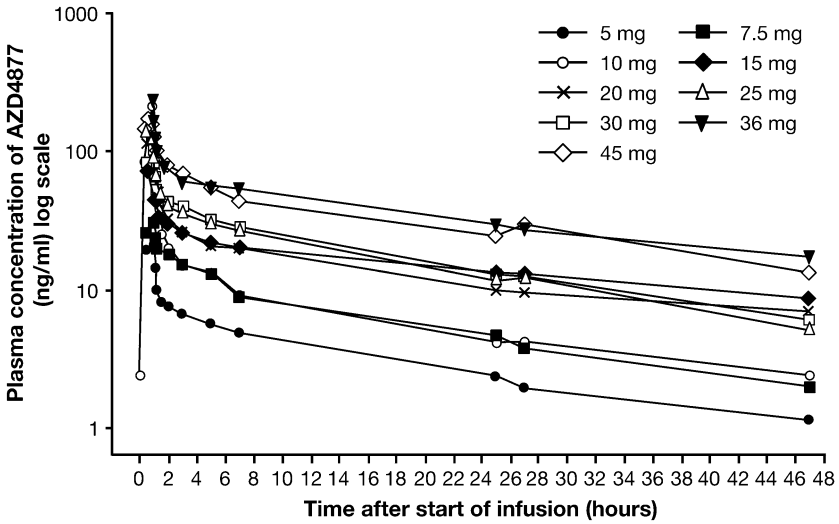

Fig. 1 Geometric mean plasma concentrations of AZD4877 versus time by AZD4877 dose level on day 1 of cycle 1

refers to patient number. Monoaster frequency ranged from 0.07 to 0.4 per 10,000 PBMCs. At AZD4877 doses <20 mg, monoasters were only observed at 6–8 h post-dose, and monoasters were only seen in patients in the AZD4877 25- or 30-mg dose group at the 6- to 8-h time point. However, monoasters were observed at the 24-h time point in at least one patient in the 20-, 36-, and 45-mg dose groups. An image of monoaster formation from a representative patient is shown in Fig. 3.

Efficacy

Of the 41 patients available for radiographic assessments, none experienced a complete or partial response. Of 11 patients with SD, seven had SD ≥12 weeks, and six of these seven had received AZD4877 at doses of ≥20 mg. The longest duration of SD was 46.6 weeks, reported in a single patient with pancreatic cancer in the 45-mg dose group. There was no apparent association between tumor type and response.

Discussion

The MTD of AZD4877, given as a 1-h iv infusion for 3 of 4 weeks, was identified as 30 mg in patients with advanced solid tumors. AZD4877 doses >30 mg were intolerable primarily due to neutropenia, the most commonly reported DLT in the study. However, there were more dose modifications and omissions during cycle 1 in the 30-mg dose cohort than in the 20-mg cohort. Because of this and the similarity in exposure between AZD4877 20 and 30 mg doses, an intermediate dose of 25 mg was selected for further evaluation in part B, the expansion phase of the study.

At a dose of 25 mg, AZD4877 was tolerable, although neutropenia was the most common AE reported by six of 14 patients (42.9%) at this dose level. Furthermore, two patients in the expansion phase of the study experienced neutropenia-related DLTs. Intracycle dose omissions and reductions still occurred in the 25-mg cohort, but at a lower frequency than in the MTD (30 mg) cohort. Despite the high frequency of neutropenia, the duration of the events was short, and the neutropenia was always reversible. As expected with an Eg5 inhibitor, no neuropathy was reported in patients treated with AZD4877 in this study.

Systemic exposure to AZD4877 was approximately dose proportional, supporting an approximately linear PK profile. The half-life of AZD4877 was approximately 16 h, and clearance was comparable across the doses evaluated. The severity of neutropenia in the study population was related to exposure to AZD4877. Monoaster formation, which is pathognomonic of Eg5 inhibition, was observed in circulating PBMCs at doses of AZD4877 >5 mg, demonstrating proof of mechanism of AZD4877. Increasing doses of AZD4877 were associated with the detection of monoasters at the 24-h time point, in addition to the 6- to 8-h time point, although no monoasters were observed in the 25- and 30-mg cohorts at the 24-h time point. The detection of monoasters at the 24-h time point in the 20-, 36-, and 45-mg dose cohorts signified a prolonged target effect of AZD4877 at these doses.

The best response to AZD4877 in this study was SD ≥12 weeks, which was observed in seven patients, six of whom received ≥20 mg doses of AZD4877. The patient who experienced the longest duration of SD (46.6 weeks) received AZD4877 45 mg. This limited clinical response is similar to what has been reported for other Eg5 inhibitors [20–25] and stands in contrast to the preclinical efficacy demonstrated by Eg5 inhibitors in mouse tumor xenograft

Table 4 Summary of AZD4877 pharmacokinetic parameters following dosing on day 1 of cycle 1

Parameter, geometric mean (CV%) [number of patients evaluated]	AZD4877									
	Part A									Part B
	5 mg ($n = 4$)	7.5 mg ($n = 4$)	10 mg ($n = 3$)	15 mg ($n = 1$)*	20 mg ($n = 4$)*	30 mg ($n = 6$)	36 mg ($n = 3$)	45 mg ($n = 3$)		25 mg ($n = 14$)
C_{max} (ng/ml)	23.1 (45.8) [3]	32.0 (47.8) [3]	58.7 (113) [2]	81.4 [1]	145 (16.5) [2]	102 (41.6) [6]	166 (48.5) [2]	254 (43.4) [3]		170 (83.9) [13]
$C_{24\ h}$ (ng/ml)	2.45 (20.7) [3]	4.76 (46.4) [3]	6.34 [1]	–	14.1 (19.9) [2]	13.1 (36.5) [6]	29.6 (39.0) [3]	25.2 (7.3) [2]		11.5 (41.0) [11]
$AUC_{0-\infty}$ (ng h/ml)	198 (19.0) [2]	341 (51.7) [2]	597 [1]	–	–	915 (11.8) [4]	–	1,890 [1]		984 (35.9) [7]
AUC_{0-24} (ng h/ml)	114 (24.7) [3]	203 (37.4) [3]	303 (49.5) [2]	511 [1]	692 (26.8) [2]	662 (23.0) [6]	1,420 (55.4) [2]	1,250 (14.5) [3]		708 (37.5) [13]
$t_{½}$ (h)†	17.0 (2.47) [2]	16.7 (2.93) [3]	17.6 (3.06) [2]	–	–	16.2 (2.46) [4]	21.2 [1]	19.7 [1]		14.5 (3.66) [7]
MRT (h)	23.3 (7.38) [2]	23.8 (7.19) [2]	16.1 [1]	–	–	19.7 (16.1) [4]	–	22.8 [1]		16.0 (29.2) [7]
V_{SS} (l)	589 (26.2) [2]	524 (45.3) [2]	270 [1]	–	–	647 (18.9) [4]	–	543 [1]		342 (58.2) [7]
CL (l/h)	25.3 (19.0) [2]	22.0 (51.7) [2]	16.7 [1]	–	–	32.8 (13.1) [4]	–	23.8 [1]		21.4 (59.1) [7]

$AUC_{0-\infty}$, area under the plasma concentration–time curve from zero to infinity; AUC_{0-24}, area under the plasma concentration–time curve from zero to 24 h; $C_{24\ h}$, plasma drug concentration 24 h after administration of a given dose; *CL*, total body clearance of drug from plasma; C_{max}, maximum plasma (peak) drug concentration after single dose administration; *CV*, coefficient of variation; *MRT*, mean residence time; $t_{½}$, half-life; V_{SS}, volume of distribution at steady state; –, mean not calculable

* One patient who was assigned to the 15-mg cohort received 20 mg in error on cycle 1, day 1. On cycle 1, day 8, this patient received 15 mg; however, results from this patient's first dose (20 mg) are included in the results for the 20-mg cohort. In addition, one patient assigned to the 15-mg cohort, received 12.86 mg and there are no cycle 1, day 1, PK samples from this patient

† For $t_{1/2}$, data are presented as arithmetic mean (standard deviation)

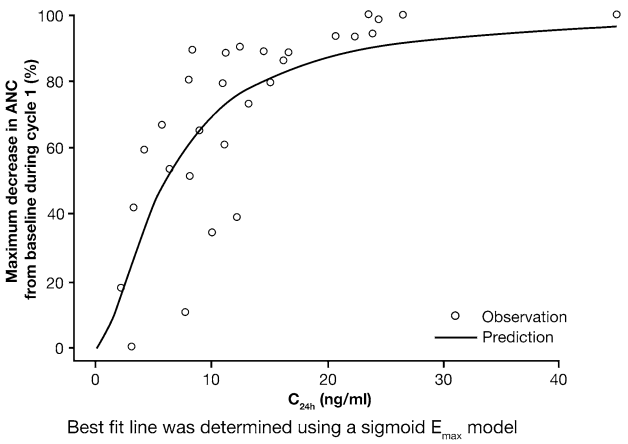

Fig. 2 Observed and predicted maximum percentage decrease in absolute neutrophil count (ANC) from *baseline* during cycle 1 versus $C_{24\ h}$

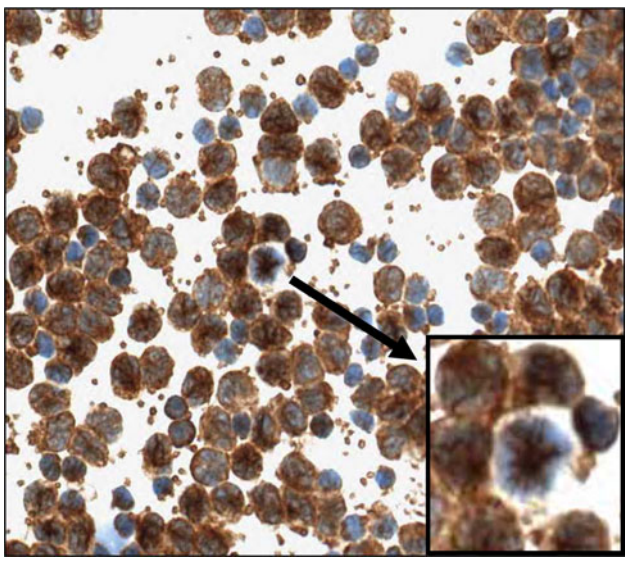

Fig. 3 Image of monoaster formation from a representative patient in the AZD4877 10-mg cohort at 6–8 h post-treatment (*arrow* indicates a monoastral cell)

models. This may indicate a much narrower, and insufficient, therapeutic window in humans relative to mice. Assessment of monoaster formation and apoptotic response in post-treatment tumor samples would facilitate a more complete understanding of tumor response to AZD4877 treatment.

In conclusion, treatment with AZD4877 appears feasible in patients with advanced solid malignancies. The primary clinical toxicity was dose-related neutropenia, which was expected from preclinical toxicology and is consistent with the findings of clinical trials with other Eg5 inhibitors [20]. Furthermore, there was evidence of monoaster formation, which was indicative of the proof of mechanism for Eg5 inhibition. However, the best response

to AZD4877 was only SD. Based on the relative lack of clinical efficacy findings in this and other completed Phase I and II trials of AZD4877, further development of this agent in oncology is not planned.

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