A Phase I Trial of AT9283 (a Selective Inhibitor of Aurora Kinases) in Children and Adolescents with Solid Tumors: A Cancer Research UK Study

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Abstract

Purpose: A phase I trial of AT9283 (a multitargeted inhibitor of Aurora kinases A and B) was conducted in children and adolescents with solid tumors, to identify maximum-tolerated dose (MTD), safety, efficacy, pharmacokinetics, and pharmacodynamic (PD) activity.

Experimental Design: AT9283 was administered as a 72-hour continuous intravenous infusion every 3 weeks. A rolling-six design, explored six dose levels (7, 9, 11.5, 14.5, 18.5, and 23 mg/m²/d). Pharmacokinetic and PD assessments, included inhibition of phospho-histone 3 (pHH3) in paired skin punch biopsies.

Results: Thirty-three patients were evaluable for toxicity. There were six dose-limiting toxicities and the MTD was 18.5 mg/m²/d. Most common drug-related toxicities were hematologic (neutropenia, anemia, and thrombocytopenia in 36.4%, 18.2%, and 21.2% of patients), which were grade ≥ 3 in 30.3%, 6.1%, and 3% of patients. Nonhematologic toxicities included fatigue, febrile neutropenia and ALT elevation. One patient with central nervous system–primary neuroectodermal tumor (CNS-PNET) achieved a partial response after 16 cycles and 3 cases were stable for four or more cycles. Plasma concentrations were comparable with those in adults at the same dose level, clearance was similar although half-life was shorter (4.9 ± 1.5 hours, compared with 8.4 ± 3.7 hours in adults). Inhibition of Aurora kinase B was shown by reduction in pHH3 in 17 of 18 patients treated at ≥11.5 mg/m²/d.

Conclusion: AT9283 was well tolerated in children and adolescents with solid tumors with manageable hematologic toxicity. Target inhibition was demonstrated. Disease stabilization was documented in intracranial and extracranial pediatric solid tumors and a phase II dose determined. Clin Cancer Res; 21(2): 267–73. ©2014 AACR.

Introduction

Cancer is the commonest cause of death in children above 1 year of age (1), and there is an urgent need to develop new therapies to improve survival and reduce the burden of long-term toxicities.

Aurora kinases are a family of enzymes that are key regulators of mitosis. They comprise Aurora A (involved in centrosome separation and maturation and bipolar spindle assembly) and Aurora B (“chromosome passenger protein”; mediating chromosome segregation and cytokinesis and phosphorylation of a number of targets, including histone H3), which have been shown to act as oncogenic drivers in a number of human cancers (2, 3). The preclinical rationale supporting the clinical development of Aurora kinase inhibitors in children with solid tumors is particularly strong because: (i) the target is dysregulated in a number of high-risk malignancies such as neuroblastoma, medulloblastoma, central nervous system primitive neuroectodermal tumor (CNS-PNET), and malignant glioma; (ii) there is a mechanistic justification of its indispensable role in MYC/MYCN-driven cancers such as neuroblastoma; (iii) there are in vitro and in vivo efficacy data, including in genetically engineered murine models; (iv) there are several drugs under development; and (v) pharmacodynamic (PD) biomarkers are available to demonstrate target inhibition in patients (4–10). AT9283 is a multitargeted inhibitor against Aurora A and B, JAK2 and ABL kinases, and has been tested in phase I/II trials in adults with solid and hematologic cancers (11–15).

This first-in-child phase I study of AT9283 in relapsed/refractory solid tumors was designed to incorporate PD and...
Translational Relevance

Aurora kinases have been shown to be highly relevant targets for several high-risk pediatric solid tumors, such as neuroblastoma in which they play a critical role in stabilization of MYCN. We here report the first-in-child phase I trial of AT9283, the first dual inhibitor of Aurora A and B kinases tested in pediatrics. Pharmacodynamic (PD) biomarkers are rarely performed in pediatric trials but are pivotal for successful drug development. In this trial, paired skin biopsies demonstrated inhibition of Aurora kinase B in the majority of patients treated above the 9 mg/m²/d dose level, hence providing proof-of-principle that PD biomarkers can be incorporated to pediatric phase I trials without causing significant risks to the patients.

Materials and Methods

Patient eligibility

Patients were included according to the following criteria: age ≥2 and <19 years, performance status Lansky ≥70% for those aged 1 to 12 years (≥50% for children with CNS tumors and stable neurologic deficits) or WHO 0, 1, or 2 for those aged ≥12 years, life expectancy of at least 12 weeks, histologically proven solid tumor refractory to conventional treatment (relapsed/progressive typical diffuse pontine glioma allowed without histologic verification), adequate bone marrow function (Hemoglobin ≥9 g/dL, absolute neutrophil count ≥1,000/μL, and platelet count ≥100,000/μL unsupported) and biochemistry (creatinine kinase normal, ALT/AST <1.5 upper limit of normal, measured glomerular filtration rate [GFR] ≥60 mL/min/1.73 m²) and written informed consent.

Exclusion criteria were: radiotherapy, endocrine therapy, or chemotherapy within the previous 4 weeks, patients with CNS tumors on an unstable or increasing dose of corticosteroids, prior exposure to an Aurora kinase inhibitor, unrecovered toxicity from prior therapies, pregnant or lactating women, unprotected sex, history of concomitant cancer, drugs that could interfere with AT9283 pharmacokinetics biomarkers, and thereby provide a "pharmaceutical audit trail" of this novel agent in children and adolescents enrolled in the trial (16).

Pharmacokinetic analysis

Blood samples were collected during screening and 4, 24, 48, 70, 73, 76, and 96 hours after the start of the infusion of cycle 1. Plasma was separated, immediately frozen at −20°C and then analyzed to determine the concentration of AT9283 using a previously developed the LC/MS method. Pharmacokinetic data were analyzed by noncompartmental methods using WinNonlin Version 5.3. Area under the plasma concentration–time curve (AUC0–t), maximum concentration achieved (Cmax), time to maximum concentration (Tmax), and elimination half-life (T1/2) for AT9283 were calculated.

Dose escalation, drug schedule, and assessments

First dose level was 7 mg/m²/d for 3 days, 80% of the adult solid phase I trial MTD (15). For each subsequent dose level, the dose was increased by up to a maximum of 30%. Body surface area was calculated according to the Mosteller formula.

AT9283 was supplied by Astex as a lyophilized solid for reconstitution in 20 mL vials that were stored at 15°C to 25°C. Vials were reconstituted to a total volume of 100 mL in 5% dextrose. AT9283 was administered i.v. continuously over 72 hours as three separate 24-hour infusions on days 1 to 3 of a 21-day cycle. Treatment was scheduled for 6 cycles, although extension could be considered for patients with stable or responding disease in which the benefit–risk balance was acceptable.

At screening, history, developmental status, performance status, physical examination, full blood count, biochemistry, urinalysis, electrocardiogram, echocardiogram, measured GFR, pregnancy test, and baseline imaging were obtained. Patients had clinic visits, physical examination, full blood count, and biochemistry weekly throughout the study treatment. Urinalysis, echocardiograms, and response assessments were performed every 2 cycles. An off study visit was performed 28 days after the last dose of AT9283. Disease evaluations included cross-sectional imaging according to RECIST 1.0 (18) and to the International Neuroblastoma Response Criteria (INRC; ref. 19) for those patients with neuroblastoma. Complete or partial responses (CR or PR) had to be confirmed by a repeat scan no less than 4 weeks after the criteria for response were first met. All stable disease (SD) responses had to meet SD criteria at least once and at least 6 weeks after study treatment was initiated.

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Pharmacodynamic studies

**Immunohistochemical markers.** Skin biopsies for PD analysis by immunohistochemistry were collected at baseline and at 72 hours, in cycle 1. The 72-hour time point was chosen based on preclinical data. Sections (3–4 μm) from paraffin-embedded specimens were mounted on poly-L-lysine-coated glass slides. After rinsing with three changes of xylo for deparaffinization, the sections were incubated for 5 minutes in 3% H2O2, and were then rinsed with PBS. Specimens were incubated for 1 hour with the lyophilized monoclonal anti–phospho-histone 3 (pH3; Cell Signalling Technology) at a dilution of 1:100; Ki67 (Zymed) at a 1:100 dilution and p53 (DAKO) at a 1:50 dilution. Immune complexes were subsequently treated with post primary block and then detected by the SuperPicTure Polymer Detection Kit (Invitrogen). Proliferating cell nuclear antigen detection was performed following the kit instructions (Invitrogen). Positive controls consisted of tissue specimen sections of breast carcinoma with known antigenic reactivity. A negative control was stained by omitting the primary antibody. The prepared specimens were stained with hematoxylin (Sigma), mounted, and evaluated using AnalySIS Software—Imaging Software (license no. A1534700). Images were captured under ×20 magnification, using the "touch count" function to count positively stained cells in the epidermal layer of the skin section.

**M30-M65 ELISA in plasma.** Blood samples for PD analysis were collected at time 0, 22, 46, 70, and 168 hours, following the start of the infusion, in cycles 1. The M30 apoptosisen and M65 ELISA kits were both obtained from PEVIVA AB (Bromma), and these assays, previously validated, were performed under dedicated Good Clinical Laboratory Practice conditions. Background variation for M30 and M65 antigens was considered in the ground variation for M30 and M65 antigens was considered. Good Clinical Laboratory Practice conditions. Back-ground variation for M30 and M65 antigens was considered.

**Results**

**Patient characteristics**

Thirty-three patients were enrolled from October 2009 until December 2012. Twenty-two of the 33 patients (66.7%) were female. The median age of patients was 9 years (range, 3–18 years). Patient characteristics are provided in Table 1. All 33 patients enrolled at least one administration of AT9283. Six-dose levels were explored: 7, 9, 11.5, 14.5, 18.5, and 23 mg/m²/d and 103 cycles were delivered. Figure 1 depicts recruitment at all six-dose levels. Dose was escalated until it reached 23 mg/m²/d where the first 2 patients experienced a DLT. The last 2 patients were already in the screening period when the two DLTs were encountered: The first one received the dose below (18.5 mg/m²/d) and developed a DLT, so the final patient was dosed at the subsequent lower dose (14.5 mg/m²/d).

**Toxicities**

Six DLTs were observed: grade 4 neutropenia lasting ≥7 days in 3 patients (14.5, 18, and 23 mg/m²/d dose levels), grade 3 febrile neutropenia in 2 children (11.5 and 23 mg/m²/d) and grade 3 suspected bacterial infection in one case (18.5 mg/m²/d). All patients who experienced DLT recovered from them sufficiently to permit their continued treatment with AT9283 at a reduced dose level. The maximum administered dose of AT9283 was 23 mg/m²/d and the MTD was established at 18.5 mg/m²/d for pediatric solid tumors.

All 33 patients enrolled in the study were evaluated for safety. Thirty-two of the 33 patients (97.0%) who received treatment with AT9283 during the study presented with at least one treatment emergent AE, and 24 of 33 patients (72.7%) presented with at least one AE that was considered by the investigator to be related to AT9283. Twenty patients (60.6%) experienced at least one serious AE (SAE), 2 of whom had to withdraw from the study as an outcome of the SAE. Twelve patients (36.4%) had at least one CTCAE grade 4 or 5 AE, and 8 patients (24.2%) died during the study, two of unrelated SAEs (neurologic impairment and raised intracranial pressure) and 6 of disease progression. Drug-related toxicities are represented in Table 2. Most common related hematologic toxicities were neutropenia in 25 episodes per 12 patients, which were grade 3 to 4 in 18 episodes per 10 patients. Febrile neutropenia occurred in 5 episodes per 4 patients. Most common nonhematologic toxicities were fatigue (5 episodes/5 patients), rash (5 episodes/3 patients), vomiting (3 episodes/3 patients), ALT elevation (5 episodes/4 patients), and fever (3 episodes/3 patients).

**Antitumor activity**

A median of 2 cycles was administered (range, 1–30). Twenty-three patients were evaluable for response. Twenty-one patients had measurable disease according to RECIST v1.0. One patient with CNS-PNET experienced a confirmed PR according to RECIST v1.0 after 16 cycles of AT9283. At the time of this report, the patient has had 30 cycles and the response is sustained. Nine other patients (37.5% of patients evaluable for response) had stabilization of their disease after two courses, with three of these achieving SD for four or more courses of AT9283 [1 patient with ependymoma (4 cycles), 1 with CNS-PNET (6 cycles), and 1 with alveolar soft part sarcoma (4 cycles)]. The 3 patients with neuroblastoma were also assessed with the International Neuroblastoma Response Criteria (19): 1 patient with MYCN-amplified disease experienced progressive disease, and 2 patients with MYCN-nonamplified disease achieved a mixed response and no response.

**Pharmacokinetics**

Plasma samples were taken for all 33 patients treated with AT9283 and were evaluable in 32 patients (97%). AT9283 plasma pharmacokinetic parameters are summarized in Table 3. Beyond the first dose level Cmax and AUC seemed to plateau and a consistent relationship between plasma concentrations and dose was not observed. In pediatric patients, plasma concentrations were comparable with those seen in adults at the same dose level, clearance was similar although half-life was shorter (4.9 ± 1.5 hours, compared with 8.4 ± 3.7 hours in adults) as shown in Table 3. Volume of distribution in pediatric patients was similar to adult cases. Clearance was not predicted by body surface area. High intrapatient variability was observed (coefficient of variation in AUC >50% at 9 and 11.5 mg/m²/d dose levels). Figure 2
represents the AUC in the different dose levels. For comparison, values for AUC in the adult phase I were 1,730/C6 550 ng/mL/C1 that 9 mg/m²/d.

Pharmacodynamic biomarkers
PD activity of AT9283 was confirmed by inhibition of pHH3 Ser10 in skin of 6 of 7 patients treated at 14.5 mg/m²/d and all 12 patients treated at 11.5, 18, and 23 mg/m²/d. Figure 3 and Supplementary Material summarize immunohistochemical findings in skin biopsies. The results for the proliferation marker Ki67 in patients treated at 14.5 mg/m²/d and below were variable, although the majority of the patients still exhibited target inhibition measured by pHH3 inhibition. In those patients treated at 18.5 and 23 mg/m²/d all patients showed reduction in Ki67-positive cells, indicating an antiproliferative effect of AT9283 at high doses. p53 may be stabilized as a direct result of inhibition of Aurora kinase A or as a consequence of cell-cycle arrest. In skin biopsies, as surrogate for tumor tissue, results on p53-positive cells showed high variability and no direct dose-dependent effect was observed.

Of a total of 16 patients evaluated, 11 displayed an increase in M30 levels during the infusion of AT9283, the maximum increase was detected at different time points and it was not dose dependent. In most of the cases, M30 levels returned to predose levels before subsequent infusions. A further 5 patients showed no increase of M30 levels during infusion. M65 levels remained constant in most of the patients analyzed (Supplementary Figure). M30:M65 data do not support a clear dose–response relationship.

Discussion
This phase I is the first of a dual Aurora A/B kinase inhibitor in childhood cancer. AT9283 is a multitargeted inhibitor against Aurora A and B, JAK2 and ABL kinases and in this pediatric phase I study was well tolerated in a heavily pretreated population of children ages 3 to 18 years with expected DLTs of febrile neutropenia or grade 4 neutropenia. The toxicity profile was similar, but the MTD was significantly higher in the pediatric study (18.5 mg/m²/d) compared with the adult (9 mg/m²/d) solid tumor study using the same dosing schedule (15). Pharmacokinetic analysis revealed that plasma concentrations and clearance were similar to those in adults, with a shorter half-life and similar volume of distribution. AT9283 was given as a 72-hour infusion every 3

![Figure 1](https://example.com/f1.png)

Figure 1. Trial recruitment and dose-escalation schema. Black dots, patients experiencing DLTs. Patients 32 and 33 had already started screening when the two DLTs in the 23 mg/m²/d dose level occurred. Patient 32 was then started at 18.5 mg/m²/d and experienced a DLT; thus, patient 33 was treated at 14.5 mg/m²/d.
weeks, which required an inpatient stay for these young patients, and to try and impact less on the child's quality of life in the future, portable continuous infusion pumps could be considered. Although oral Aurora kinase inhibitors have been developed, pediatric-friendly formulations in appropriate doses are not always available, and intravenous preparation and regimens may still play a role in young children.

This study included mandatory PD analyses pre- and post-study drug exposure that had been investigated in prior preclinical and adult clinical studies (11–15, 20). These included skin punch biopsy samples as a surrogate tissue, and even with a pediatric population this PD analysis was successfully completed and demonstrated inhibition of Ser10 phosphorylation in histone H3 and inhibition of Aurora kinase activity even at the lowest

| Table 3. Summary of pharmacokinetic parameters |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Dose level, mg/m²/d | Number of patients | Cmax (ng/mL) | AUCₐ₀₋½ (ng·h/mL) | Half-life (h) | CL (L/h) | Vss (L) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 7               | 5               | 7.0–19.0         | 639 ± 385       | 5.7 ± 0.4       | 39.7 ± 25.6    | 328 ± 180     |
| 9               | 5               | 14.7–68.5        | 1,817 ± 1,246   | 4.9 ± 1.5       | 20.4 ± 7.7     | 158 ± 74      |
| 11.5            | 6               | 14.5–68.8        | 2,102 ± 1,074   | 5.1 ± 1.2       | 22.3 ± 15.1    | 157 ± 122     |
| 14.5            | 7               | 14.8–60.6        | 2,267 ± 938     | 5.2 ± 2.0       | 20.0 ± 6.8     | 114 ± 72      |
| 18.5            | 7               | 17.3–80.9        | 1,946 ± 799     | 5.6 ± 1.5       | 37.8 ± 16.4    | 224 ± 79      |
| 23              | 2               | 631–89.0         | 3,436–5,303     | 4.0–18.7        | 20.9–19.6      | 256–363       |

Abbreviations: CL, drug clearance; Vss, volume of distribution at steady state.
dose levels, consistent with plasma levels and activity observed in in vitro models. Neither the Ki67 assay in skin nor the analysis of M30:M65 levels in plasma were informative in this study and probably reflect the differences between childhood and adult cancers. In the adult population, epithelial cancers predominate whereas pediatric malignancies are mainly of mesenchymal origin, and thus do not express CK18, the cleavage of which is the basis of the M30:M65 assay. This illustrates that the choice of biomarkers is not only related to the mechanism of the study drug, but should include consideration of the tumor context and age of the patient. At the time of the design of the study there were no validated predictive tumor biomarkers for Aurora kinase inhibitors, and therefore analysis of tumor tissue was not included. This was a weakness of the study and several putative biomarkers have emerged, which would have been of interest to study in terms of interrogating responders versus nonresponders. Possible exploratory biomarkers include; disturbance of cell-cycle checkpoint function, for example, p53 deficiency, or uncontrolled cell-cycle entry, that is, loss of pRB or MYC overexpression (3). In preclinical studies, AT9283 induced a cell-cycle checkpoint in cells with wild-type p53 status, returning to the regular cell cycle once AT9283 administration was withheld, whereas checkpoint-incompetent tumor cells (i.e., p53 deficient), underwent endoreduplication and apoptosis (20).

A third of evaluable patients had initial stabilization of their disease (SD) after two cycles with 3 patients maintaining SD beyond four cycles. Another patient with a CNS-PNET experienced a confirmed PR according to RECIST v1.0 after 16 cycles of AT9283 and at the time of the report has had 30 cycles with a sustained response. This and a maintained SD in 2 other patients with brain tumor indicate that AT9283 does reach sufficient levels in the CNS to have an effect. These results are similar to the only other reported pediatric Aurora kinase inhibitor study, in which there was 1 PR and 6 SD of 23 patients with measurable disease treated with the Aurora A selective inhibitor MLN8237 (21).

Aurora kinase inhibitors have so far failed to make a major impact in adult solid tumors with more promising activity being seen in hematologic malignancies (lymphoma and leukemia; refs, 22, 23). Pediatric results indicate that Aurora kinase inhibition is achieved with tolerable doses of AT9283, but as in the adult studies this has not translated into objective responses in the majority of cases. Better patient selection with biomarker enrichment based on p53, pRB, and MYC status along with possible combination strategies such as other antimitotic inhibitors or signal transduction inhibitors would be valuable strategies for future studies.

This pediatric phase I study of AT9283 demonstrated significant Aurora kinase inhibition at tolerable doses with disease stabilization demonstrated in a variety of childhood solid tumors. Future studies will focus on hematologic malignancies and possible combination studies in solid tumors.
Disclosure of Potential Conflicts of Interest

I. Moreno is a consultant/advisory board member for AstraZeneca, Novartis, and Roche/Genentech. J.F. Lyons is an employee of Astex Pharmaceuticals. No potential conflicts of interest were disclosed by the other authors.

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References


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