A Phase 1 Open-Label, Accelerated Dose-Escalation Study of the Hypoxia-Activated Prodrug AQ4N in Patients with Advanced Malignancies

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Abstract

**Purpose:** AQ4N is a novel prodrug that is selectively bioreduced to AQ4, a topoisomerase II inhibitor, in hypoxic tumor. This study assessed the maximum tolerated dose and pharmacokinetics of AQ4N when administered weekly in patients with advanced cancers.

**Experimental Design:** AQ4N was administered as a 30-minute i.v. infusion on days 1, 8, and 15 of a 28-day cycle in eight dose cohorts ranging from 12 to 1,200 mg/m². Accelerated titration design was used and the maximum tolerated dose was defined as the highest dose at which fewer than two of six patients had a dose-limiting toxicity.

**Results:** Sixteen patients were treated with cumulative doses of AQ4N ranging from 61.6 through 9,099.1 mg/m². A single patient per cohort was treated up to 384 mg/m² without toxicities. At 1,200 mg/m², two of five patients experienced a dose-limiting toxicity (grade 5 respiratory failure and grade 3 fatigue). Five cohort assigned patients were treated without toxicity at 768 mg/m², establishing this dose as the maximum tolerated dose. Among the most common adverse events observed were fatigue (38%), diarrhea (31%), nausea (25%), vomiting (25%), and anorexia (13%). Anticipated blue coloration of body fluids or skin was observed in all patients. The pharmacokinetics of AQ4N were dose proportional over all doses studied. Three patients experienced stable disease, including a patient with collecting duct renal cancer stable for 25 months.

**Conclusion:** AQ4N is well tolerated when administered weekly on a 3-of-4-week schedule at 768 mg/m². Further combination studies investigating the safety and efficacy of AQ4N are ongoing.

Hypoxia is characteristic of solid tumors and mediates, in part via hypoxia-inducible factor-1, changes in transcriptional regulation of genes involved in cellular metabolism, survival, angiogenesis, and metastasis (1–6). Prolonged tumor hypoxia increases genomic instability and treatment resistance, selects for metastatic variants, and has been shown to influence disease progression in preclinical and clinical studies (1–7).

AQ4N (baxoxantrone; 1,4-bis[2-(dimethylamino)ethyl]amino)-5,8-dihydroxanthracene-9,10-dione bis-N-oxide) is rationally designed as a prodrug that is preferentially converted to a potent cytotoxin in hypoxic tumor regions (8–11). The prodrug form of AQ4N is relatively nontoxic to cells until it is bioreduced in hypoxic tumor cells by a two-step enzymatic reduction to form AQ4M, a short-lived mono-N-oxide intermediate, and then to the ditertiary cationic amine, AQ4 (11–14). AQ4, but not AQ4N, binds DNA with high avidity and functions as a potent inhibitor of topoisomerase II (14). Bioreduction of AQ4N occurs strictly in the absence of oxygen and seems to be catalyzed by a number of cytochrome P450 enzymes, which are commonly up-regulated in tumors (15–20).

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Antitumor response when AQ4N is combined with chemotherapy and/or radiation (8, 22–27).

Animal toxicology studies have established repeated doses of AQ4N at 20 mg/kg/wk in rats and 6 mg/kg/wk in monkeys as the maximum tolerated dose when given for 6 consecutive weeks. AQ4N toxicity was consistent with that of a cytotoxin targeting the lymphoid system, gastrointestinal tract, and urogenital tract, indicating differences in the conversion of AQ4N to AQ4 or differences in sensitivity in these tissues. There was also dose-related blue discoloration of skin and urine.

Single and limited repeat dosing of AQ4N have been explored previously in two clinical trials. A phase 1 trial of administration of a single dose of AQ4N (200 mg/m²) before elective surgery in 32 cancer patients confirmed selective activation of AQ4N in hypoxic regions of tumors (28). In another phase 1 trial of 22 patients with advanced esophageal carcinoma who had been clinically assessed as being inoperable and not eligible for chemotherapy, AQ4N was administered i.v. on day 1, followed by a second dose at the same dose level on day 15 given 6 hours before the first of 6 consecutive weeks. AQ4N toxicity was consistent with that of a cytotoxin targeting the lymphoid system, gastrointestinal tract, and urogenital tract, indicating differences in the conversion of AQ4N to AQ4 or differences in sensitivity in these tissues. There was also dose-related blue discoloration of skin and urine.

Study assessments. Baseline assessment included a complete medical history, physical examination, laboratory tests, urinalysis, electrocardiogram, multiple gated acquisition scan, and radiographic imaging. Toxicities were evaluated at each visit with appropriate cardiac monitoring before each odd cycle. Computed tomography scans for assessment of tumor burden were obtained at baseline and infused i.v. over ~30 min.

Pharmacokinetic evaluation. Serial blood samples for plasma pharmacokinetics of AQ4N and its metabolites were collected on days 1 and 15 of the first cycle at the following time points: predose and post-AQ4N infusion at 2 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, and 24 h. Urine for analysis was collected over designated intervals for 24 h after the first dose of AQ4N and frozen before analysis. AQ4N and its two bioreduced metabolites AQ4, AQ4M, and AQ4 were quantified from frozen heparinized plasma samples using validated high-performance liquid chromatography with tandem mass
spectrometric methods as previously described (31, 32). In brief, AQ4N, AQ4M, and AQ4 were extracted from plasma samples using MCX SPE well plates (Waters Corp.). Aliquots of the extracts were analyzed by reverse-phase high-performance liquid chromatography (Agilent Technologies) using an Astec Polymer C18 column maintained at 50°C. The mobile phase was nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds were detected using a tandem quadrupole Quatro II mass spectrometer (Micromass, Inc.). The lower limit of quantitation was 10 ng/mL for AQ4N and AQ4M and 2 ng/mL for AQ4 in human plasma. Noncompartmental analysis was used to evaluate the overall pharmacokinetics using WinNonlin Professional 4.1 (Pharsight, Inc.). Pharmacokinetic variables that were assessed included maximum plasma concentration (C\text{max}), area under the plasma concentration versus time curve from time to infinity (AUC\text{0-\infty}), elimination half-life (t\text{1/2}), volume of distribution at steady-state (V\text{ss}), and plasma clearance (CL\text{p}). Pharmacokinetic variables are expressed as mean and SD except for half-life, which is presented as the harmonic mean and pseudo-SDs.

### Results

**Patient characteristics.** Sixteen patients, whose pertinent demographic characteristics are shown in Table 1, were enrolled in the study between September 2004 and March 2006. Patients were treated with cumulative doses of AQ4N ranging from 61.6 through 9,099.1 mg/m², escalated through eight sequential dose level cohorts; the median number of cycles administered per patient was 2 (range, 1-27). All patients were evaluable for toxicity and response.

**Dose escalation and serious adverse events.** A single patient per cohort was evaluated at AQ4N doses of 12, 24, 48, 96, 192, and 384 mg/m², and five patients each were evaluated at doses of 768 and 1,200 mg/m² (Table 2). Grade 2 drug-related toxicities were observed at the 768 mg/m² dose level and three patients were initially evaluated. Dose-limiting toxicities of grade 3 fatigue and fatal grade 5 respiratory failure occurred respectively in two patients following treatment at 1,200 mg/m². The fatal respiratory failure was probably related to postmortem findings of extensive progressive metastatic sarcoma, including myocardial and pulmonary organ involvement. As a consequence of these toxicities, dose reduction to 768 mg/m² was done in three of the patients actively receiving therapy in the 1,200 mg/m² cohort, and the 768 mg/m² cohort was further expanded. No dose-limiting toxicities or drug-related serious adverse events were observed in any of the five cohort-assigned and three dose-reduced patients treated at the 768 mg/m² level, and this dose level was identified as the maximum tolerated dose.

**Toxicity.** Toxicities reported in at least 10% of patients and all grade 3 and 4 toxicities in all cycles are summarized in Table 3. Among the most common drug-related adverse events observed were fatigue (38%), diarrhea (31%), nausea (25%), vomiting (25%), and anorexia (13%). Nausea, vomiting, and diarrhea were grade 1 or 2 and managed with medication. Anticipated blue coloration of skin and body fluids was observed in all patients at doses ≥48 mg/m² or with prolonged dosage (Table 3). The duration of skin discoloration was predicated by the dose and extent of therapy, usually lasting <24 to 72 hours. Transient blurred vision occurred in two patients at 1,200 mg/m², and eye irritation was reported by

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
<th>Median age (range), y</th>
<th>Sex (male/female)</th>
<th>Race (White/Black/Hispanic)</th>
<th>Performance status</th>
<th>Prior therapies</th>
<th>Chemotherapy regimens, median (range)</th>
<th>Anthracyclines</th>
<th>Radiation therapy</th>
<th>Tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>16</td>
<td>57 (32-80)</td>
<td>8/8</td>
<td>10/3/3</td>
<td>0</td>
<td>16</td>
<td>3 (1-10)</td>
<td>4</td>
<td>5</td>
<td>Lung</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Renal cell</td>
<td></td>
<td></td>
<td>Prostate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prostate</td>
<td></td>
<td></td>
<td>Head and neck</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Breast, cervical, colon, hepatocellular, ileum, melanoma, ovarian, sarcoma</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

### Table 2. AQ4N treatment by dose level

<table>
<thead>
<tr>
<th>Dose level (mg/m²)</th>
<th>No. of patients</th>
<th>No. of cycles (range)</th>
<th>Cumulative dose* (mg/m²)</th>
<th>No. of patients with DLT</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1</td>
<td>1</td>
<td>61.6</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>24</td>
<td>1</td>
<td>2</td>
<td>144.2</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>48</td>
<td>1</td>
<td>27</td>
<td>3,621.9</td>
<td>0</td>
<td>1 SD</td>
</tr>
<tr>
<td>96</td>
<td>1</td>
<td>2</td>
<td>556.5</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>192</td>
<td>1</td>
<td>2</td>
<td>1,105.1</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>384</td>
<td>1</td>
<td>1</td>
<td>1,143.3</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>768</td>
<td>5†</td>
<td>2 (1-2)†</td>
<td>3,815.0†</td>
<td>0</td>
<td>1 SD</td>
</tr>
<tr>
<td>1,200</td>
<td>5</td>
<td>2 (1-3)†</td>
<td>4,376.9†</td>
<td>2 [grade 3 fatigue (1); grade 5 respiratory failure (1)]</td>
<td>1 SD</td>
</tr>
</tbody>
</table>

Abbreviations: DLT, dose-limiting toxicity; SD, stable disease.

*Total includes partially completed cycles.
†Excludes three dose-reduced patients treated at the 768 mg/m² level.
‡Based on a median of five patients.
two patients treated at 192 and 384 mg/m². Myeloid and lymphoid suppression was dose dependent, generally mild, and not associated with clinical sequelae except in one patient receiving AQ4N at 48 mg/m², who after 25 cycles of therapy developed persistent pancytopenia. With one exception, patients evaluated with serial electrocardiogram (n = 16) and multiple gated acquisition scan (n = 10) every two cycles of treatment or at study discontinuation showed no evidence of significant electrocardiogram changes or cardiac dysfunction. A patient with a history of diabetes, hypertension, ischemic heart disease, and previous myocardial infarction and angioplasty was treated at 192 mg/m² of AQ4N and had a 13% decline in ejection fraction to 43% after two cycles of therapy. This event was not attributed to AQ4N following further cardiac evaluation.

Pharmacokinetics. The first-dose pharmacokinetic variables of AQ4N in 16 patients are summarized in Table 4. Following i.v. administration, AQ4N plasma concentrations declined rapidly in a multieponential manner and there was no drug accumulation after repeated dosing (Fig. 1A). The C_max and AUC incremented proportionally with increasing dose level (Fig. 1B and C). The mean clearance (CL_p) of AQ4N for all patients was 3.09 L/h/m², and although CL_p ranged from 1.69 to 4.45 L/h/m² across dose groups, the overall clearance values were relatively constant. The mean volume of distribution at steady state (Vss) for the 16 patients completing pharmacokinetic evaluation was 11.48 ± 3.29 L/m². Both variables seemed to be independent of dose. The harmonic mean terminal elimination half-life for all dose levels was 4.10 ± 2.29 hours. Following i.v. administration of AQ4N, plasma concentrations of the intermediate mono-N-oxide AQ4M metabolite were appreciably lower (<5%) than the parent AQ4N prodrug. Although AQ4M concentrations declined in a somewhat parallel fashion to AQ4N, there was considerable fluctuation in the declining plasma concentrations, and determination of the terminal t_{1/2} was not possible for most patients. Due to the limited number of patients evaluated in each dose group and the considerable variability in data across and within doses, a dose-relationship for AQ4M C_max and AUC could not be assessed. Plasma concentrations for the fully bioconverted metabolite, AQ4, were below assay quantification limits (< 2.00 ng/mL) in the majority of the samples, with most quantifiable samples <5.00 ng/mL. Overall, urinary excretion of AQ4N accounted for ~70% of the administered AQ4N dose over the first 24 hours. At lower doses (12-192 mg/m²), the percent of AQ4N excreted in urine ranged from 14% to 47% of the dose, whereas urinary excretion in the 368 to 1,200 mg/m² dose groups accounted for 78% to 94% of their respective doses. In all dose groups, the majority of the dose excreted in urine was recovered during the first 10 hours following dose administration. The renal clearance of AQ4N ranged from 16.52 to 108 mL/min across all dose groups and seemed to be dose dependent with clearance values >50 mL/min at doses ≥192 mg/m².

Tests for correlations of AQ4N dose and pharmacokinetic variables AUC_C∞ and C_max with toxicity were done. Except for a nonsignificant trend for cytopenia with increasing drug dose, no correlation for toxicities was apparent (data not shown).

Antitumor activity. No responses were observed, with 13 patients progressing. There were three patients with stable disease, including two patients with bronchoalveolar lung cancer and ovarian cancer. One patient with collecting duct renal cancer treated with AQ4N at 48 mg/m² had prolonged disease stabilization for 25 months.

Discussion

AQ4N is designed to be an inactive prodrug in normal tissues but to be selectively activated to a potent cytotoxin in hypoxic

### Table 3. Related adverse events occurring in >10% of patients and all Common Toxicity Criteria for Adverse Events grade 3-5 in patients treated with AQ4N

<table>
<thead>
<tr>
<th>Chromaturia</th>
<th>Skin discoloration</th>
<th>Fatigue</th>
<th>Diarrhea</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Anorexia</th>
<th>Abdominal discomfort</th>
<th>Eye irritation</th>
<th>Blurred vision</th>
<th>Alopecia</th>
<th>Respiratory failure</th>
<th>Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 (100)</td>
<td>13* (81)</td>
<td>6 (38)</td>
<td>5 (31)</td>
<td>4 (25)</td>
<td>4 (25)</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>1 (6)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>[1 (6)]</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Not reported in two patients from the <48 mg/m² cohorts and one patient of African American heritage from the 1,200 mg/m² cohort.

### Table 4. AQ4N noncompartmental pharmacokinetic variables on day 1 of cycle 1 following infusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>12</th>
<th>24</th>
<th>48</th>
<th>96</th>
<th>192</th>
<th>384</th>
<th>768</th>
<th>1,200</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>5.3</td>
<td>2.3</td>
<td>2.1</td>
<td>3.4</td>
<td>3.5</td>
<td>4.5</td>
<td>3.6 ± 0.6*</td>
<td>4.1 ± 1.5*</td>
</tr>
<tr>
<td>C_max (ng/mL)</td>
<td>1,720</td>
<td>4,382</td>
<td>7,374</td>
<td>13,457</td>
<td>28,440</td>
<td>50,660</td>
<td>98,415 ± 23,635</td>
<td>144,556 ± 37,088</td>
</tr>
<tr>
<td>AUC_{ss} (ng/mL)</td>
<td>7,092.0</td>
<td>6,609</td>
<td>12,320</td>
<td>44,376</td>
<td>65,115</td>
<td>153,801</td>
<td>242,282 ± 70,032</td>
<td>485,034 ± 291,176</td>
</tr>
<tr>
<td>CL_p (L/h/m²)</td>
<td>1.69</td>
<td>3.63</td>
<td>3.90</td>
<td>2.16</td>
<td>2.95</td>
<td>2.50</td>
<td>3.39 ± 0.97</td>
<td>2.97 ± 1.07</td>
</tr>
<tr>
<td>Vss (L/m²)</td>
<td>10.47</td>
<td>8.38</td>
<td>9.05</td>
<td>8.66</td>
<td>9.83</td>
<td>13.15</td>
<td>11.32 ± 2.73</td>
<td>13.49 ± 4.54</td>
</tr>
</tbody>
</table>

*Data are presented as median ± SD, except for half-life, which is expressed as harmonic mean ± pseudo-SD (34).
In this phase 1 study of AQ4N, dose-limiting toxicities (i.e., fatigue and respiratory failure) were observed at 1,200 mg/m². The patient with fatal respiratory failure had extensive cardiac and pulmonary involvement with sarcoma that likely contributed to her death. Five cohort assigned patients were enrolled at an AQ4N dose of 768 mg/m² without dose-limiting toxicity, and this dose was established as the maximum tolerated dose. Aside from fatigue, nonhematologic and hematologic toxicities of grade ≥2 severity were uncommon and AQ4N was generally well tolerated. Noteworthy is that although anticipated skin-related toxicity occurred across all dose cohorts ≥48 mg/m², this was largely cosmetic. Previous dose-finding studies were limited and suggested good tolerance of AQ4N (29). Except for skin discoloration, no drug-related adverse events were noted in 22 patients following a single 22.5 to 447 mg/m² dose of AQ4N (29). Combination with radiation following a second dose of AQ4N made attribution of adverse events difficult in this prior study. Similarly, AQ4N-related adverse events in a single 200 mg/m² dose study included skin discoloration and fatigue but few other drug-related toxicities (28). One patient with ischemic heart disease in this latter study had a myocardial infarction and left ventricular failure thought to be possibly drug related. AQ4N is similar in structural to anthracenedione antineoplastic agents, which are known to result in reduced cardiac function following high cumulative dosing. There was no evidence of change in electrocardiogram, decline in ejection fraction, or myocardial dysfunction in the current study to suggest acute cardiotoxicity from higher cumulative doses of AQ4N.

Pharmacokinetic data from this phase 1 trial showed that AQ4N exhibits dose-proportional kinetics over the dose range tested. Plasma concentrations of the bioreduced active metabolites, AQ4M and AQ4, were appreciably lower (<5% for AQ4M) or undetectable (for AQ4). The lack of systemic activation of AQ4N is consistent with its prodrug mode of action. Previous preclinical and clinical studies have confirmed that AQ4N seems to be selectively metabolized into its active form, AQ4, in hypoxic regions of tumors but not in normal healthy tissues (21, 22, 27–29, 33). The majority of administered AQ4N undergoes rapid renal excretion during the first 10 hours following dose administration. Plasma levels achieved at the maximum tolerated dose with this weekly dosing are sufficient for antineoplastic activity reported in preclinical models (28). Although no objective antitumor response to AQ4N was observed in patients in this phase 1 study, three patients (collecting duct renal cell, ovarian, and bronchoalveolar lung cancer) had stable disease.

In conclusion, the maximum tolerated dose of AQ4N administered on days 1, 8, and 15 of a 28-day cycle is 768 mg/m². The low toxicity of this weekly dosing schedule in this patient population together with prior demonstration of tumor selectivity and hypoxia targeting of AQ4N, particularly in glioblastoma multiforme (28), provides the basis for rationally designed monotherapy and combination studies. Weekly AQ4N in combination with radiation therapy and temozolomide is currently under evaluation in patients with newly diagnosed glioblastoma multiforme.

**Disclosure of Potential Conflicts of Interest**

A. Wong, M. Milian, and A. Lalani are former employees of Novacae, Inc.
References

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