Phase 1 Study of Aldoxorubicin + Gemcitabine in Metastatic Solid Tumors

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Abstract

Background: Aldoxorubicin (A) is a novel prodrug of doxorubicin that binds covalently to the cysteine-34 residue of endogenous albumin within a few minutes. The reaction follows second-order kinetics. Aldoxorubicin is a prodrug of the anticancer agent doxorubicin which is derivatized at its C-13 to albumin, accumulates in tumors and releases D under acidic conditions. It has demonstrated significant efficacy against soft tissue sarcomas in a phase 2b study versus D. The primary objective of this study is to determine the preliminary safety of administration of A+ G on Days 1 and 8 of each 21 day cycle. Safety was monitored continuously, cardiac function was assessed using either MUGA or cardiac ultrasound.

Objectives

• The primary objective of the study is to evaluate the safety of administration of Aldoxorubicin and gemcitabine in combination with gemcitabine in the population, assessed by CNI, PFS and ORR in 12 months.

Materials and Methods:

1. Study Design

This is a Phase 1b, open-label study evaluating the preliminary safety and activity of Aldoxorubicin at eddiation of 170, 250, 200 mg/m2 and Gemcitabine at 900 mg/m2 every 21 days plus 500 mg/m2 gemcitabine on Day 1 every 21 days. A subsequent dose level of aldoxorubicin plus gemcitabine was administered if < 2 of 3 or < 4 of 6 subjects experience a DLT during Cycles 1 and 2.

2. Study Endpoints

- Safety: Inclusion of 6 subjects per dose level is based on the assumption that a dose level 90% confidence level of 95% for the probability of the occurrence of any grade 3 or 4 AE that limits dosing.

- Efficacy: Tumor response until disease progression or when the patient is not evaluable.

- Toxicity: A subsequent dose level of Aldoxorubicin + Gemcitabine was administered if < 2 of 3 or < 4 of 6 subjects experience a DLT during Cycles 1 and 2.

3. Study Population

Eligible subjects were 70 years or younger, had histologically verified metastatic solid tumors, with one or more lesions measurable by CT and patients with ECOG of 0-2. Patients with Brain metastases and prostate cancer were not eligible. Patients were required to have a life expectancy >12 weeks.

4. Study Outcomes

- Tumor Response: Complete and partial response

Statistical Analysis:

1. Continuous variables are expressed as median and range or mean and standard deviation when normally distributed. Categorical variables are expressed as number and percentage.

2. Results will be presented as median and range for continuous variables and number and percentage for categorical variables.

3. Formal statistical inference was not performed due to small number of patients.

4. Safety: Tumor response until disease progression or when the patient is not evaluable.

5. Toxicity: A subsequent dose level of Aldoxorubicin + Gemcitabine was administered if < 2 of 3 or < 4 of 6 subjects experience a DLT during Cycles 1 and 2.

Study Results

1. Patient Characteristics:

<table>
<thead>
<tr>
<th>Aldoxorubicin (mg/m2)</th>
<th>Gemcitabine (mg/m2)</th>
<th>Complete Response</th>
<th>Partial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>170</td>
<td>900</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>250</td>
<td>900</td>
<td>1 (12.5)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>200</td>
<td>900</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>200</td>
<td>500</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

2. Adverse Events:

- Grade 3/4 Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>N 9 4 9 5**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>1 (11)</td>
</tr>
<tr>
<td>launcher thrombosis</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

3. Cardiac Evaluation:

- Life expectancy >12 weeks.

4. Serious Adverse Events

- SAEs associated with aldooxubicin or both include: febrile neutropenia (2), neutrophenia (2), anemia (1). No treatment-related deaths have occurred.

5. Conclusions:

- Doses of 200 mg/m2 aldoxorubicin + 500 mg/m2 gemcitabine appears to be feasible.

References:


**Abstract**

Glioblastoma (GBM) is the most common and aggressive of all primary brain tumors. Approximately 60% of all gliomas are diagnosed each year, and GBM accounts for about 45% of these malignancies. Without treatment, survival is only approximately 14 months after diagnosis. Unfortunately, virtually all patients relapse regardless of the initial therapy and median survival of ~14 months after initial therapy. Despite numerous and relatively well-tolerated, and demonstrated anti-tumor activity in patients with relapsed GBM.

Aldoxorubicin is a pH-sensitive prodrug of doxorubicin (D) and is attached to a C-13 keto-position with a thiol-binding spacer molecule (6-maleimidocaproic acid). Aldoxorubicin was administered to 2 cohorts at doses of 250 mg/m² and 350 mg/m². The study was an open-label, single-arm, phase II study to evaluate the safety of aldoxorubicin in this patient population. Aldoxorubicin-related SAEs included febrile neutropenia (1), mucositis (1), oral candidiasis (1), somnolence (1), seizure (1). No treatment-related deaths occurred.

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**Key Eligibility Criteria**

**Age**: 18 or older. **Male or female.**

**Histopathology or cytopathologically confirmed GBM.** Subjects with recurrent disease who prior pathology demonstrated GBM will not be re-biopsied.

**Karnofsky performance status**: 0-100.

**Life expectancy**: 3 or more months.

**No prior exposure to an anthracycline.**

**Proposed Mechanism of Action**

Aldoxorubicin is quantitatively and selectively bound to the cysteine-34 position of endogenous albumin within a few minutes of administration. The reaction follows a first-order rate kinetic and is irreversible. Aldoxorubicin-related SAEs included febrile neutropenia (1), mucositis (1), oral candidiasis (1), somnolence (1), seizure (1). No treatment-related deaths occurred.

**Objective**

**The primary objective of this study is to determine the preliminary efficacy of administration of aldoxorubicin to subjects with unresectable GBM whose tumors have progressed following treatment with surgery, radiation therapy and temozolomide, as measured by PFS as per the RANO Working Group Criteria and OS.**

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Aldoxorubicin is a prodrug of the antitumor agent doxorubicin which is rapidly metabolized by cytochrome CYP2D6 to doxorubicin (DOX) and doxorubicin aldehyde (DOXAL). Aldoxorubicin is quantitatively and selectively bound to the cysteine-34 derivative at its C-13 keto-position with a thiol-binding spacer molecule (6-GM-MB) have treated 15 patients with KS with low dose A and monitored tumor response, disease events and accruals of A to the tumor and peritumoral lesions. Of the 15 patients entered in the study, there had received prior systemic cytotoxic chemotherapy1:

- Grade 3+ Adverse Events Related to Aldoxorubicin

AEs: left leg abscess, leukopenia, VRE decreased, hypertumouria.

Conclusions

- A randomized phase II study for well-tolerated, grade 3–4 AE risks for CTD cells (RA), neutropenia (22%), and overall AEs (44%) comparing favorably with AZ risks from other trials enrolling KS patients, including advanced and symptomatic population.

References


