A Phase I trial of AVA6000, a Fibroblast Activation Protein (FAP)-released and tumor microenvironment (TME)-targeted doxorubicin peptide drug conjugate in patients with FAP-positive solid tumors

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BACKGROUND AND PRECLINICAL DATA

MECHANISM OF ACTION OF AVA6000

Fibroblast activation protein (FAP) is an extracellular matrix protein that is upregulated in many solid tumors in a membrane-bound form on cancer-associated fibroblasts as well as tumor cells. FAP activity is also observed as a soluble factor in the plasma in cancer patients. AVA6000 is a peptide drug conjugate that leverages the tumor-specific expression of FAP by targeting peptide moieties (specifically cleaved by FAP) to doxorubicin.

The peptide moiety linking the doxorubicin to the FAP inhibitor CDSYN prevents cellular entry of doxorubicin unless cleaved by FAP, thus enabling targeted delivery of doxorubicin to tumors.

IN VIVO CHARACTERIZATION OF AVA6000

The antitumor activity of AVA6000 was assessed in two in vivo xenograft models, one with low and one with high tumor plasma FAP activity. As shown in Fig. 2 (left panel), the model with a low activity ratio (HPAF 1, TME) has limited antitumor activity against a high FAP activity in Fig. 2 (right panel), suggesting that patients with tumors with a high activity ratio are more sensitive to the inhibition of FAP activity by AVA6000.

CLINICAL TRIAL METHODS

AVA6000 was assessed in a multi-center, ascending dose Phase 1 trial in patients with solid tumors. The patient population included the following:

- Patients with a diagnosis of known FAP+ cancers, including colorectal cancer, pancreatic cancer, ovarian cancer, and biliary tract cancer
- Acceptable performance status (0-1)
- Adequate hematologic, hepatic, and renal function
- Prior therapy with any antineoplastic limited to one line of therapy prior to enrollment
- Patients with tumors that demonstrate high FAP activity

For patients, hematologic and non-hematologic AEs were assessed at the following time points: before dose (day -1), on day 1, and weeks 2, 4, 6, 8, and 10. Pharmacokinetics was assessed at the following time points: day 1: before dose and 1, 2, and 4 hrs post-dose; and week 2: before dose and 1 hr post-dose.

RESULTS

SAFETY

BASELINE CHARACTERISTICS

Table 1. Demographics and Baseline Cancer History

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>AVA6000 200mg/m2</th>
<th>AVA6000 400mg/m2</th>
<th>AVA6000 600mg/m2</th>
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<td>Age (years)</td>
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<td>56</td>
<td>56</td>
<td>60</td>
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<tr>
<td>Gender (%)</td>
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<td>55/45</td>
<td>55/45</td>
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<tr>
<td>Race (%)</td>
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</tr>
<tr>
<td>Black (%)</td>
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</tr>
<tr>
<td>Other (%)</td>
<td>5</td>
<td>5</td>
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</tbody>
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PATIENTS WITH FAP+ ACTIVITY OF AVA6000 IS OBSERVED IN FAP+ TUMOR MODELS

FIGURE 2. ENHANCED ANTI-TUMOR ACTIVITY OF AVA6000 IS OBSERVED IN FAP+ TUMOR MODELS

Study duration: 16 weeks

INDICATIONS

The utility of AVA6000 was explored in a Phase I trial in patients with a variety of solid tumors (Table 2). AVA6000 was administered in patients with colorectal carcinoma, pancreatic cancer, ovarian cancer, biliary tract cancer, transitional cell cancer of the urethra, small cell lung cancer, prostate cancer, transitional cell cancer of the bladder, and sarcoma.

PHARMACOKINETICS/PHARMACODYNAMICS

The pharmacokinetics of AVA6000 were assessed in the Phase I trial. The sum of the plasma exposure of doxorubicin (AVA6000) and free doxorubicin was quantitated with a fluorescent D-2-Serine amide reference standard. The pharmacokinetics of AVA6000 in patients was assessed at the following time points: day 1: before dose and 1, 2, and 4 hrs post-dose; and week 2: before dose and 1 hr post-dose.

Efficacy data was collected and analyzed using the published reference standard PK of doxorubicin (at 75 mg/m2). These data were analyzed using the published reference standard PK of doxorubicin (at 75 mg/m2).

CONCLUSIONS

AVA6000 delivers high concentrations of doxorubicin to the TME in patients with FAP+ tumors, resulting in significant antitumor activity in patients whose tumors have over-expression of FAP.

AVA6000 has a distinct safety profile, with significant reductions in both severe and mild to moderate toxicities associated with standard dose doxorubicin.

Exposure-response modeling suggests that released doxorubicin is generated primarily by cleavage in the TME as opposed to soluble FAP in the bloodstream.

PK/PD modeling demonstrates separation of the probability curves for response v. grade 3-4 neutropenia, supporting the further exploration of the Q2W dosing regimen.

Further development at the recommended dose for expansion (RDE) is planned in 2H 2024 in specific tumor types with high FAP expression and antiangiogenic sensitivity.