ABSTRACT

Background: In many tumors, extracellular adenosine contributes to an immunosuppressed tumor microenvironment via activation of the A$_2$A receptor (A$_2$AR) and A$_2$B receptor (A$_2$BR) expressed on intratumoral immune cells. AB928 is a novel, selective, small-molecule antagonist of both A$_2$AR and A$_2$BR with the ability to potently block the immunosuppressive effects of high concentrations of adenosine in the tumor microenvironment. Preclinically, combining adenosine receptor inhibition with either chemotherapy or anti-programmed cell death-1 (PD-1) has resulted in greater tumor control in mouse models, suggesting that AB928 may have synergistic activity when paired with either chemotherapy or checkpoint inhibitors in oncology patients. A phase 1 study with AB928 in healthy volunteers has been completed.

Methods: A phase 1/1b, open-label, dose-escalation (3+3 design) and dose-expansion study was designed to evaluate the safety/tolerability (including dose-limiting toxicities (DLTs), pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of AB928 in combination with standard of care (SOC) carboplatin/pemetrexed (carbo/pem) plus pembrolizumab (pembro) in patients with nonsquamous non-small-cell lung cancer (NSCLC). Patients are eligible if they have pathologically confirmed nonsquamous NSCLC that is metastatic or recurrent with progression. Patients may have received up to 5 lines of prior therapies in dose escalation and up to 3 lines of prior therapies in dose expansion. AB928 is administered orally once daily at a starting dose of 75 mg (Cohort 1) escalating to 150 mg (Cohort 2) and 200 mg (Cohort 3), and carbo/pem plus pembro is administered at the standard regimen (carbo: AUC of 75 mg (Cohort 1) escalating to 150 mg (Cohort 2), and 200 mg (Cohort 3)). Intermediate AB928 doses may be evaluated based on data from cohorts that have been explored. Doses that have exceeded the maximum tolerated dose (MTD) will not be evaluated. Following identification of the recommended phase 2 dose (RP2D) of AB928 in combination with carbo/pem plus pembro during dose escalation, the lung cancer cohort will be expanded to further evaluate this combination. The combination of AB928 and carbo/pem without pembro may also be evaluated in dose expansion. The primary endpoint is safety/tolerability and secondary endpoints are PK (receptor occupancy in peripheral blood and immunomodulatory activity in select immune subsets), and clinical activity (objective response rate (ORR), duration of response, disease control rate (DCR), complete response (CR), partial response (PR), or stable disease (SD) for >6 months), and progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and overall survival. FDA submission completed with start-up for recruitment ongoing.

Figure 1. Adenosine-mediated immune suppression

- The accumulation of adenosine, generated through hydrolysis of extracellular adenosine monophosphate (AMP) by the ectonucleotidase CD73, is a key strategy exploited by tumors to escape immune surveillance (Figure 1)\(^1\). Adenosine’s suppressive effects on immune cells are driven primarily by 2 of the 4 adenosine receptors, A$_2$AR and A$_2$BR:
  - This effect is mediated by increased cyclic AMP (cAMP) levels and phosphorylation of cAMP response element binding protein (CREB)
  - Pharmacological inhibition of the effects of adenosine has recently generated much interest in immuno-oncology, but thus far, only A$_2$AR antagonists, initially developed for central nervous system indications,\(^3\) are being studied in oncology

Figure 2

- AB928 is a novel, selective, small-molecule A$_2$AR/A$_2$BR antagonist designed to potently block the immunosuppressive effects of high concentrations of adenosine in the tumor microenvironment
- AB928 differs from other known A$_2$AR antagonists based on its dual mode of action, its minimal loss of potency due to nonspecific binding to plasma proteins, and its lack of penetration through a healthy blood-brain barrier
- In mouse models, combining adenosine receptor inhibition with either chemotherapy (Figure 2) or anti-PD-1 resulted in greater tumor control, suggesting AB928 may have synergistic activity when combined with either chemotherapy or checkpoint inhibitors in cancer patients
  - This is supported by the literature showing that cancer cells treated with chemotherapy induce immunosuppressive cell death, characterized by upregulation of CD39/CD73 leading to enhanced adenosine generation

METHODS

- Four clinical studies of AB928 in combination with other agents have been initiated in cancer patients in Australia and United States (Table 1)
- The study described herein (AB928CSP0004) is assessing the safety/tolerability, PK, PD, and clinical activity of AB122 (PD-1 inhibitor) monotherapy and AB928 in combination with carbo/pem plus pembro (SOC)\(^3\) or carbo/pem in patients with NSCLC

Table 1. Ongoing AB928 combination studies in oncology

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Combination</th>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB928CSP0002</td>
<td>AB928 + PLD (SOC)</td>
<td>TNBC or Ovarian</td>
</tr>
<tr>
<td>AB928CSP0003</td>
<td>AB928 + mOLFFOX (SOC)</td>
<td>GEC or CRC</td>
</tr>
<tr>
<td>AB928CSP0004</td>
<td>AB928 + Carbo/Pem (SOC)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>AB928CSP0005</td>
<td>AB928 + Carbo (240 mg Q2W)</td>
<td>Solid tumors</td>
</tr>
</tbody>
</table>

Figure 2. Tumor control with AB928 + doxorubicin (A) or oxaliplatin (B) in mouse model

- A phase 1 study of AB928 in healthy volunteers has been completed
  - This placebo-controlled study with single-ascending and multiple-ascending dose arms assessed AB928 doses between 10 and 200 mg once daily and 100 mg twice
  - AB928 was well tolerated and no safety concern was identified
    - All adverse events (AEs) were Grade 1/2; there were no DLTs, serious AEs, or AEs resulting in study drug discontinuation
    - The PK profile of AB928 was linear and dose-proportional, and a clear PK/PD correlation was demonstrated (Figure 3)
    - AB928 plasma levels ≥1 μM were associated with >90% adenosine receptor inhibition

Figure 3. PK/PD correlation in AB928-dosed subjects measured by pCREB inhibition

- ORR and DCR will be estimated by the proportion of patients with objective response and disease control, respectively, and their 95% confidence intervals will be calculated using the exact binomial method
- Time-to-event endpoints will be summarized using the Kaplan-Meier method
- Summary statistics will be provided for AEs, serious AEs, AE severity, and relationship to study drug
- PK parameters will be estimated using noncompartmental methods
- ORR and DCR will be estimated by the proportion of patients with objective response and disease control, respectively, and their 95% confidence intervals will be estimated using the exact binomial method
- Interim analyses for futility will be conducted for each expansion cohort that has enrolled ≥15 patients who are evaluateable for disease assessment

Trial Status

- Enrollment ongoing

REFERENCES