156P: A Phase 1b/2 Study of Nanatinostat (Nstat) Plus Valganciclovir (VGCV) in Advanced Epstein-Barr Virus Positive (EBV+) Solid Tumors and with Pembrulimab (PMB) in Recurrent/Metastatic Nasopharyngeal Carcinoma (PM-NPC)

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**Background**

- EBV is linked to the pathogenesis of NPC; high pre-treatment plasma EBV DNA (pEBV) levels and slow clearance are associated with inferior outcomes.**1**
- EBV is predominantly latent in NPC, induction of the viral lytic phase by histone deacetylase inhibitors (HDACs) renders EBV+ tumor cells susceptible to the cytolytic activity of ganciclovir (GCV).
- Nanatinostat (Nstat) is a potent oral Class I HDAC that induces the EBV lytic cycle in EBV+ NPC cells (Figure 1) and expression of the lytic BGLF4 protein kinase, activating GCV on phosphorylation. GCV-triphosphate becomes incorporated into cellular DNA, resulting in chain termination and apoptosis.**2**
- Targeting EBV with Nstat and valganciclovir (VGCV), the oral prodrug of GCV, in NPC represents a novel therapeutic approach.
- The RP2D of Nstat 20 mg 4 days/week plus VGCV 900 mg daily was well-tolerated and demonstrated clinical activity in a phase 1b/2 study in patients with R/R EBV+ lymphoma.**3**
- This phase 1b/2, open-label, multicenter study is evaluating the safety, pharmacokinetics and preliminary activity of the oral all combination of Nstat + VGCV in patients with advanced EBV+ solid tumors.
- Additionally, the combination of Pembrulimab (PMB) together with Nstat + VGCV will be evaluated in RM-NPC patients. Figure 1. Nanatinostat induces the EBV lytic cycle in NPC cells

**Methods**

- **Key Eligibility Criteria**
  - EBV RM-NPC: 1 prior line of platinum-based chemotherapy (max. 3 prior lines of therapy) and no curative options.
  - Phase 1b dose expansion cohort: Advanced/metastatic EBV+ non-NPC solid tumors with no available curative therapies.
  - Measurable disease per RECIST v1.1.
  - No anti-tumor cytotoxic drugs, biologic therapy, immunotherapy, or other investigational drugs in 4 weeks or ≤5 half lives.
  - No active CNS disease.
  - Plasma EBV DNA (≥10,000 IU/mL).
  - Treatment plasma PK concentration similar to Nstat 20 mg (Fig. 2).

- **Safety**
  - The majority of treatment-related adverse events (TRAEs) were classified as mild/moderate (Table 3); no DL3 were reported in the first 3 dose levels.
  - One SAE was reported (cancer pain), unrelated to study drug. Table 1. Treatment-related adverse events in ≤3 patients

- **Pharmacokinetics**
  - PK concentration-time curves for Nstat for DL1 and DL2 patients (Figure 3) indicated a dose-dependent increase in exposure. Exposure at 20 mg was similar to that observed in a study of patients with relapsed/refractory EBV+ lymphoma.**4**

- **Results**
  - Data is reported on 10 patients from DL1-3 in this analysis (cut-off date 14 Nov 22).
  - The baseline characteristics of the patients are presented in Table 2.

- **Table 2. Patient Demographics**
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DL-1 Patients (n=3)</th>
<th>DL-2 Patients (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y), (range)</td>
<td>63 (35-70)</td>
<td>64 (39-74)</td>
</tr>
<tr>
<td>Male / Female</td>
<td>2/1</td>
<td>1/5</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0-1</td>
<td>0-2</td>
</tr>
<tr>
<td>Treatment site: lung</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Prior lines of antineoplastic therapy in R/M setting (n=4)</td>
<td>1 (0-3)</td>
<td>2 (0-3)</td>
</tr>
</tbody>
</table>

- **Table 1. Phase 1b provisional dose levels (DLs)**
<table>
<thead>
<tr>
<th>Dose level</th>
<th>Dose (RP2D)</th>
<th>N</th>
<th>EBV+ NPC</th>
<th>DL1</th>
<th>DL2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;20 mg</td>
<td>10</td>
<td>20 mg</td>
<td>900 mg daily</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>20 mg</td>
<td>5</td>
<td>30 mg</td>
<td>900 mg daily</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>30 mg</td>
<td>3</td>
<td>40 mg</td>
<td>900 mg daily</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>40 mg</td>
<td>3</td>
<td>50 mg</td>
<td>900 mg daily</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>50 mg</td>
<td>3</td>
<td>60 mg</td>
<td>900 mg daily</td>
<td>4</td>
</tr>
</tbody>
</table>

- **Figure 2. Study Design**

- **Figure 3. Nanatinostat plasma concentration-time curves for DL 1 and 2 patients (n=7)**

- **Figure 4. Plasma EBV DNA Titer For Evaluable Patients (n=7)**

- **References**
  - Many TRAEs were low-grade, gastrointestinal or constitutional in nature. Enrollment to dose level 1 (Nstat 10 mg BID, 4 days per week plus VGCV 900 mg BID x 21), then QD, is anticipated to open this month, pending Safety Committee review.

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**Contact information:**

**Figure 2. Study Design**

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- **Key abbreviation:**
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