Plinabulin (Plin), a Novel non-G-CSF Molecule for the Prevention of Chemotherapy-Induced Neutropenia (CIN), has the Potential to Positively影响 Tumor Micro Environment

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Study BPI-2368-105 (NCT03102606): Phase 2/3, Multicenter, Randomized, Double Blind Study to Evaluate Duration of Severe Neutropenia with Plinabulin Versus Pegfilgrastim in Patients with Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy

Plinabulin Overview:
- Small Molecule
- Inexpensive to manufacture
- Given by IV infusion, on the same day of the chemotherapy
- More than 300 Patient Data from Phase II/III
- Currently in Phase III in NSCLC

Plinabulin is a small molecule activator of GEFH1 and represents a novel signaling pathway leading up to activation of Dendritic Cells. Plinabulin has Anti-Cancer Activity, as demonstrated previously (ASCO-BTC 2017).

Elevated Neutrophil-to-Lymphocyte Ratio (NLR) of ≥ 5 leads to Immune Suppression, and is associated with poor prognosis in cancer patients (Shi, Nature 2017).

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Plinabulin Activates Dendritic Cells

Primary objective:
To establish the Recommended Phase 3 Dose (RPD) based on PK/PD analysis.

Methods:

Assessments:
- Absolute Neutrophil Count (ANC): Lymphocyte counts and Neutrophil to Lymphocyte Ratio (NLR) were assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 6, 7, 8, 9, 10, and 15; Blood pressure was measured semi-continuously with 15-minute intervals, starting 15 minutes pre-plinabulin dose and lasting ~ 4.5 hours after start of infusion with plinabulin; Bone Pain was assessed with a validated questionnaire [Bone Pain Inventory (Short Form)]; Pharmacokinetics of plinabulin; Bone Pain was assessed with a validated questionnaire [Bone Pain Inventory (Short Form)]; Pharmacokinetics of plinabulin; Safety was evaluated through Adverse Events (AEs), Complete Blood Counts (CBC), and Hematology.

Study Design:
This was the phase 2 portion of the phase 2/3 BPI-2368-105, and was designed as a multicenter, open label, randomized study.

A total of N=55 patients were enrolled in this study. Patients were randomly assigned to the following arms:
- Arm 1: Docetaxel (75 mg/m²) + Plinabulin (20 mg/m²) (N=14); Docetaxel (75 mg/m²) + Plinabulin (20 mg/m²) (N=14); Arm 2: Docetaxel (75 mg/m²) + Plinabulin (5 mg/m²) (N=14); Docetaxel (75 mg/m²) + Plinabulin (5 mg/m²) (N=14); Arm 3: Docetaxel (75 mg/m²) + Plinabulin (6 mg/m²) (N=15); Docetaxel (75 mg/m²) + Plinabulin (6 mg/m²) (N=15)

Target Patient Population:
Patients with advanced or metastatic non-Small Cell Lung Cancer (NSCLC) after failing platinum-based therapy.

Here we report the final study results from the phase 2 portion of Study BPI-2368-105.

Key Finding:
1. Plinabulin and Pegfilgrastim Are Equally Effective for Grade 4 Neutropenia

Neutropenia by Grade by Cycle (Cycle 1)

Figure 1. Neutropenia by Grade (95% CI) (Cycle 1)

Key Finding:
1. Plinabulin-Acute Neutrophil Count Remained in Normal Range

Figure 2. Absolute Neutrophil Count (95% CI) (Cycle 1)

Neutrophil-to-Lymphocyte Ratio (NLR) by Cycle (Cycle 1)

Figure 3. Bone Pain with Plinabulin and Pegfilgrastim.

Key Finding:
1. Plinabulin caused less Bone Pain vs Pegfilgrastim

Primary objective:
To establish the Recommended Phase 3 Dose (RPD) based on PK/PD analysis.

Table 3. Plinabulin Superior Profile compared with Pegfilgrastim

<table>
<thead>
<tr>
<th>Primary Dose</th>
<th>Plinabulin</th>
<th>Pegfilgrastim</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=38</td>
<td>N=38</td>
<td>N=38</td>
</tr>
<tr>
<td>NLR</td>
<td>2.9 M</td>
<td>6.7 M</td>
</tr>
<tr>
<td>Compelling difference</td>
<td>P = 0.29</td>
<td>P&lt;0.05</td>
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</tbody>
</table>

Table 3. Plinabulin Superior Profile compared with Pegfilgrastim

Key Finding:
1. Plinabulin-Pegfilgrastim (p<0.002), and Pegfilgrastim (p<0.003) increased Lymphocyte Count relative to baseline

Lymphocyte Count by Cycle (Cycle 1)

Figure 4. Lymphocyte Count (95% CI) (Cycle 1)

Plinabulin vs. Pegfilgrastim

Plinabulin Overview:

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Plinabulin AEs
- Bone pain, splenic rupture and splenomegaly, acute respiratory distress syndrome, glomerulonephritis, and capillary leak syndrome

Compelling Safety Profile of Plin

Plinabulin: Less nausea, vomiting, diarrhea, and transient hypertension

Conclusion:

- Plinabulin is an equally effective single-dose-per cycle agent as Pegfilgrastim for CIN
- In contrast to Pegfilgrastim, Plinabulin does not increase NLR to immune-suppressive levels, and has immune-enhancing activity
- For Chemo/Immunotherapy combinations, Plinabulin could be the preferred option to prevent CIN

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