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

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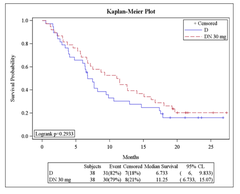
Study BPI-2358-105 (NCT03102606): Phase 2/3, Multicenter, Randomized, Double Blind Study to Evaluate Duration of Severe Neutropenia with Plinabulin Versus Pegfilgrastim in Patients with Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy

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 I,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-SITC 2017).

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



	Plinabulin + Docetaxel (DN)	Docetaxel alone (D)
	N=38	N=38
mOS	11.3 M	6.7 M
	P = 0.29	
DOR**	12.7 M	1.0 M
	P<0.05	
ORR	18.4%	10.5%
PFS	3.7 M	2.9 M

Plinabulin Activates Dendritic Cells

Primary objective:
To establish the Recommended Phase 3 Dose (RP3D) 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 were assessed with bioanalytical methods; 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-2358-105, 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/m^2) + Pegfilgrastim (6 mg) (N=14); Arm 3: Docetaxel (75 mg/m^2) + Plinabulin (10 mg/m^2) (N=13);
Arm 2: Docetaxel (75 mg/m^2) + Plinabulin (20 mg/m^2) (N=14); Arm 4: Docetaxel (75 mg/m^2) + Plinabulin (5 mg/m^2) (N=14)

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-2358-105.

Results

Neutropenia Results

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

Key Finding:

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

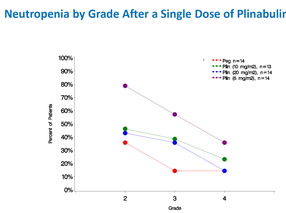
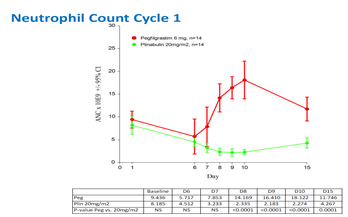


Figure 2. Absolute Neutrophil Count (95% CI) (Cycle 1)

Key Findings:

1. Plinabulin: Mean Absolute Count Remained in Normal Range
2. Pegfilgrastim: Mean Absolute Neutrophil Counts Overshoots Upper Limit of Normal

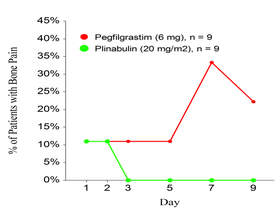


	Baseline	D6	D7	D8	D9	D10	D15
Peg	9.430	5.717	7.803	14.109	16.410	16.122	11.746
Plin 20mg/m2	8.185	4.512	3.233	2.335	2.183	2.274	4.267
P-value Peg vs. 20mg/m2	NS	NS	NS	<0.0001	<0.0001	<0.0001	0.0001

Figure 3. Bone Pain with Plinabulin and Pegfilgrastim.

Key Finding:

1. Plinabulin caused less Bone Pain vs Pegfilgrastim

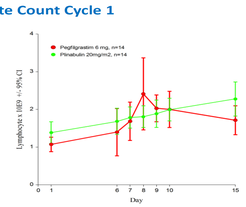


Lymphocyte Count Results

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

Key Finding:

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

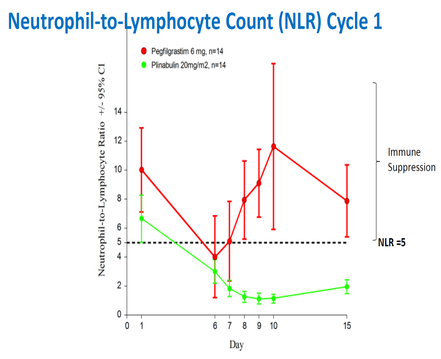


Neutrophil-to-Lymphocyte Ratio (NLR) Results

Figure 5. NLR (Cycle 1)

Key Findings:

1. Pegfilgrastim Significantly Increased NLR to >5
2. Plinabulin kept Postdose NLR <5



	Baseline	D6	D7	D8	D9	D10	D15
Peg	10.025	4.007	5.095	7.945	9.109	11.642	7.872
Plin 20mg/m2	6.665	3.011	1.829	1.261	1.128	1.150	1.960
P-value Peg vs. 20mg/m2	NS	NS	0.0425	0.0006	<0.0001	0.0043	0.0007

Plinabulin vs. Pegfilgrastim

Table 3. Plinabulin Superior Profile compared with Pegfilgrastim

Target Indication: Prevention of all chemo-induced neutropenia in all cancers

For Patients
- **High Quality of Life** (less bone pain)
- **Ease of Use** (first day dosing)

For Physicians
- **Potential for Improved Efficacy** (durable anti-cancer benefit, more chemo cycles of treatment)
- **Potentially Fewer ER Visits**

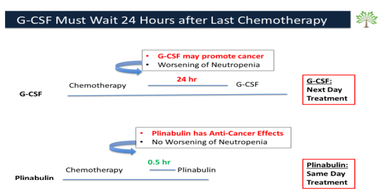
For Payers
- **Lower cost** with lower hospitalization admissions rate and duration of stay
- **Maintain pricing similar to G-CSFs**

For Production
- **Potential for large commercial opportunity** in an already-established and underserved market
- **Opportunity for significantly lower COGs** (small molecule vs. biologic)

Compelling Safety Profile To-Date

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

G-CSF AEs: bone pain, splenic rupture and splenomegaly, acute respiratory distress syndrome, glomerulonephritis, and capillary leak syndrome



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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