Plinabulin, a Novel Small Molecule Clinical Stage IO Agent with Anti-Cancer Activity, Prevents Chemo-Induced Neutropenia, and has the Potential to also Prevent Immune Related AEs.

Ramon W. Mohanlal, Douglas Blayney (Stanford University), Ken Lloyd, Lyudmila Bazhenova (UCSD), Rafael Santana-Davila (UW), Lan Huang; BeyondSpring Pharmaceuticals, New York, NY

Abstract 126

Background: Plinabulin (Plin) is a small molecule with tumor-inhibiting and immune-enhancing effects by targeting Dendritic Cells (DCs). In preclinical studies, Plin induces DC maturation and the production of MHCII, CD40, CD80 and CD86 and related antigen-specific T-cell activation. Plin had synergistic anticancer efficacy with PD1+CTLA4 inhibitors in animal models. In addition, Plin increases expression of IL-1β, IL-6, IL-12 in DC cell, which cytokines protect neutrophils against apoptosis. In a Phase 2 (Ph2) trial, the addition of Plin to Docetaxel (Plin+Doc; n = 38) in NSCLC patients (pts) with a measurable lesion, improved mOS with 4.6 mo vs Doc alone (n = 38). DOR (a marker of immune effect) was ~1 yr longer (P < 0.05) with Plin+Doc vs Doc alone. Plin exerted immune-enhancing effects (DOR), without increasing Immune-Related AEs (IR-AEs). This may suggest that Plin exerts immune-enhancing and anti-inflammatory effects.
Methods: Prospective, randomized Ph2 clinical trial (NCT00630110) and non-clinical studies.
Results: In-vitro screens showed that Plin is a PDE4-inhibitor, and clinical evidence (p < 0.03; n = 90) of PDE4-inhibition with Plin was observed in Ph2. PDE4-inhibitors have steroid-like effects and are approved for the treatment of Inflammatory disorders, and thus have the potential to prevent IR-AEs. In addition, Plin prevented chemo-induced Neutropenia (CIN), through a mechanism, different from G-CSF, in non-clinical (with various chemotherapies) and Ph2. In Ph2, Gr 4 Neutropenia occurred in 5% with Plin+Doc vs 33 % off pts with Doc (p < 0.0003) in Cycle 1, day 8. Plin is given 30 mins after chemo (on the same day of chemo), and does not cause bone pain. G-CSF is given 24 hrs after chemo, and causes bone pain in most pts.
Conclusions: Plin exerts anticancer immune-enhancing effects, combined with anti-inflammatory effects, due to PDE4-inhibition. Plin holds the promise of an agent with anti-cancer efficacy, while also mitigating IR-AEs and CIN. Therefore, Plin is an attractive candidate for combination therapy with PD1-inhibitors (or PD-L1 inhibitors), PD1+CTLA-inhibitor, or PD1-inhibitor/chemotherapy.

Methods

Plinabulin Overview:
- **Small Molecule**
- **Patent life 2038**
- **Inexpensive to manufacture**
- **Given by IV infusion, on the same day of the chemotherapy**
- **More than 200 Patient Data from Phase I,II,III**
- **Currently in Phase III**

Study BPI-2358-105
A 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.
Primary Objective Phase 2 portion:
To establish the Recommended Phase 3 Dose (RP3D) based on PK/PD analysis; PD of Efficacy is Duration of Severe Neutropenia (DSN) and Grade 4 Neutropenia.
A total of N= 55 patients with advanced or metastatic NSCLC were enrolled. Patients were randomly assigned to the following arms (with the respective sample sizes) :
Arm 1: Docetaxel (75 mg/m^2) + Pegfilgrastim (6 mg) (n=14)
Arm 2: Docetaxel (75 mg/m^2) + Plinabulin (20 mg/m^2) (n=14)
Arm 3: Docetaxel (75 mg/m^2) + Plinabulin (10 mg/m^2) (n=14)
Arm 4: Docetaxel (75 mg/m^2) + Plinabulin (5 mg/m^2) (n=13)
A second Phase 2/3 Prospective Head-to-Head comparison trial between Plinabulin and Neulasta using TAC Chemotherapy has started (Study BPI-2358-106) No data is yet available.
Investigator Initiated Studies (IIT) with Plinabulin + Nivolumab
NSCLC patients were treated with a combination of Plinabulin + Nivolumab in two separate IIT Phase 1/2 studies in patients with Non Small Cell Lung Cancer:
1. Study BPI-2358-201:
with Nivolumab (240 mg on day 1 and 15) and Plinabulin (20 and 30 mg/m2) administered on days 1 and 15 of each 28 day cycle
2. Study BPI-2358-202:
with Nivolumab (3 mg/kg on day 1 and 15) and Plinabulin (13.5, 20, 30 or 40 mg/m2) on day 1,8 and 15 administered in 28 day cycles

Study NPI-2358-101
A Phase 1/2 Study of NPI-2358 in Combination with Docetaxel in Patients with Advanced Non-Small Cell Lung Cancer
Primary objective of Study NPI-2538-101:
- Overall survival (OS)

Secondary objective of Study NPI-2358-101:
- Response Rate (RR), Duration of Response (DoR), 6-month survival, and PFS
- Safety (including Neutrophil Counts) and AEs.

Patients received Plinabulin on Days 1 and 8 of each 3-week (21-day) cycle, at 30 mg/m2 (n=50) or 20 mg/m2 (n=40).

Plinabulin — Neutropenia Reduction Data

Introduction

Clinical complications of Neutropenia (Febrile Neutropenia, Infections, Sepsis, and Mortality) occur with Grade 4 Neutropenia, as opposed to with Grade 2 or 3 Neutropenia.
For regulatory approval, the FDA and Health Authorities focus on Grade 4 Neutropenia data.
Grade 4 Neutropenia/Severe Neutropenia is an Absolute Neutrophil Count of <0.5x10E9/L.

Figure 1: Percentage of Patients with Grade 4 Neutropenia with Docetaxel +/- Plinabulin.

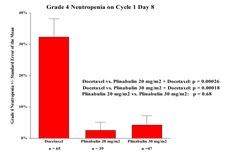


Table 1. Plinabulin has a Superior Product Profile vs G-CSF/Neulasta

	G-CSF	Plinabulin
Therapy Type	Growth Factor	Anti-cancer agent
Bone Pain (% of patients)	> 20%[1]	<4%
Hospitalization (% of patients)	20%	6%
Dose Administration	24 hours after chemotherapy	0.5-1 hour after chemotherapy
Therapy Type	Biologic	Small molecule

In Animal Models, Plinabulin prevents Neutropenia caused by number of Chemotherapies with different Mechanisms:
1. Docetaxel
2. Cisplatin
3. Adriamycin
4. Cyclosphosphamide
5. Topotecan
6. Gemcitabine

Table 2. Topline Prospective Neutropenia Data Phase 2 Portion of Study BPI-2358-105

Neutropenia	Neulasta 6mg N=14	Plinabulin 5 mg/m2 N=14	Plinabulin 10 mg/m2 N=14	Plinabulin 20 mg/m2 N=13
Grade 4 Incidence (%)	14%	23%	21%	15%
DSN (Days)	0.14	0.46	0.43	0.38

Conclusion

1. The 20 mg/m2 Plinabulin dose, given as a single dose 30 minutes after Docetaxel, is the most Effective Plinabulin Dose to prevent Docetaxel-Induced Neutropenia
➢20 mg/m2 Plinabulin is the recommended Phase 3 dose for study BPI-2358-105
2. Plinabulin is Non-Inferior to Neulasta for DSN in this phase 2 trial, within our pre-defined Non-Inferiority margin.

Plinabulin — Anti - Inflammatory Data

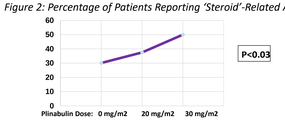
Introduction

In vitro screening demonstrated that Plinabulin is a potent inhibitor of Phosphodiesterase 4 (PDE4). PDE4 inhibitors are potent inhibitors of inflammation. PDE4 inhibiting drugs are approved for the Inflammatory disorders Eczema, Psoriasis, COPD and under development for a number of additional inflammatory disorders. PDE4-inhibitors are not steroids, but have 'steroid-like' effects. PDE4 inhibitors have the potential of preventing Immune-Related Adverse Events (IR-AEs) caused by PD1/CTLA4 inhibitors.

Indirect Evidence of PDE4-Inhibition with Plinabulin in Phase 2 at Relevant Plinabulin Doses

In the Phase 2 trial Study NPI-2358-101, Plinabulin was administered at 20 mg/m2 and 30 mg/m2 in combination with Docetaxel (75 mg/m2). All patients received docetaxel with dexamethasone peri-medication (oral dexamethasone (16 mg), Steroid-Related Adverse Events (AEs) were collected.

Figure 2: Percentage of Patients Reporting 'Steroid'-Related AEs



The Addition of Plinabulin to Dexamethasone (a Steroid), increased 'Steroid'-Related AEs dose-dependently, due to PDE4-inhibition.

Effects of Plinabulin on Immune-Related AEs from ongoing IIT studies with Nivolumab/Plinabulin combination.
In the two phase 1 studies in NSCLC patients, a total of 10 patients have been enrolled to date and received Nivolumab (240 mg or 3 mg/kg) in combination with Plinabulin 13.5 mg/m2 (n=3), or 20 mg/m2 (n=5), or 30 mg/m2 (n=2).

Two patients had developed grade 1 or grade 2 IR-AEs, without the need of Steroid treatment. No grade 3/4 IR-AEs were observed.

Conclusion

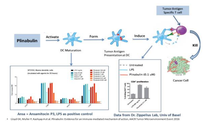
1. Plinabulin is a Potent PDE4 inhibitor, and clinically exerts 'Steroid-like' effects
2. Plinabulin is therefore a viable alternative to Steroids
3. Preliminary clinical data suggests that the addition of Plinabulin to checkpoint inhibitor therapy prevents IR-AEs

Plinabulin — Immuno-Enhancing Data

Introduction

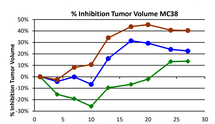
Evidence for Plinabulin's Immune Enhancing effects was demonstrated:
In Vitro Studies demonstrating that Plinabulin activates Dendritic Cells and Antigen-specific proliferation of T-Lymphocytes (Figure 3)
In-Vivo animal studies demonstrating that Plinabulin added to PD1/CTLA4-inhibitor combination has more anticancer efficacy vs checkpoint-inhibitor combination alone
Plinabulin induced a statistically significant prolongation of Duration of Response (DoR), a marker of Immune-Enhancing efficacy in a Phase 2 trial

Figure 3. Plinabulin Immune-Enhancing Mechanism of Action



R.Mohanlal Sept.2016
Biopharmadealmakers.nature.com

Figure 4: Plinabulin's Anti-Cancer Efficacy in Combination with Checkpoint Inhibitors vs Checkpoint Inhibitors Alone.



Green: PD1-Inhibitor
Blue: PD1-Inhibitor + CTLA4-Inhibitor
Brown: PD1-Inhibitor + CTLA4-Inhibitor +Plinabulin

Clinical Evidence of Plinabulin's Immune-Enhancing Effects
Prolongation of Duration of Response (DoR) is indicative of an Immune-Enhancing Mechanism.
In Study NPI-2358-101, Plinabulin added to Docetaxel prolonged DoR significantly vs Docetaxel alone (P < 0.05).

	Plinabulin +Docetaxel*	Docetaxel Alone
Duration of Response	12.7 Months	1.0 Months

*: P<0.05 Plinabulin+Docetaxel vs Docetaxel Monotherapy

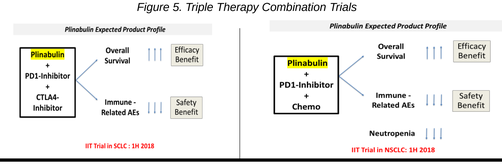
Conclusion

1. Plinabulin causes activation of Dendritic Cells and antigen-specific proliferation of T-cells
2. Plinabulin exerts Immune-Enhancing effects

Future Trials :

Plinabulin is an attractive candidate for combination therapy with PD1-inhibitors (or PD-L1 inhibitors), PD1+CTLA-inhibitor, or PD1-inhibitor/chemotherapy.
These two phase 1/2 Triple Therapy Combination Trials (see below) are in preparation by BeyondSpring Pharmaceuticals.

Figure 5. Triple Therapy Combination Trials



Final Conclusions

- **Plinabulin has Immune-Enhancing Effects and Anti-Inflammatory effects**
- **Plinabulin Prevents Chemotherapy-Induced Neutropenia**
  - **Plinabulin's DSN (duration of Severe Neutropenia) meets the criteria for Non-Inferiority to Neulasta in this prospective phase 2 trial based on the pre-defined Non-Inferiority margin. Confirmation of this result in phase 3 is awaited.**
  - **The recommended phase 3 dose (RP3D) for study BPI-2358-105 is 20mg/m2 Plinabulin.**

Contact: rmohanlal@beyondspringpharma.com