A Phase II trial with the Combination of Plinabulin (Plin) Pegfilgrastim (Peg): Evaluation of the Reversal of Peg's Immune-Suppressive Potential by the Addition of Plin to Peg

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Abstract No.4

Introduction:

- **Neutrophil-to-Lymphocyte Ratio (NLR) of > 5 is considered Immune-Suppressive and is associated with poor cancer outcome**
- **Lymphocyte-to-Monocyte Ratio (LMR) of < 3.2 is considered Immune-Suppressive and is associated with poor cancer outcome**

We previously presented that (ESMO 2018; SITC 2018):

- **Pegfilgrastim, but not Plinabulin leads to NLR > 5 and LMR < 3.2**

We previously reported that combining Plinabulin with Pegfigrastim has superior protection against Chemo-Induced-Neutropenia (CIN)

Here we evaluated if Plinabulin, when combined with Pegfilgrastim mitigates Pegfigrastim-induced NLR > 5 and LMR < 3.2

Methods

Plinabulin Overview:

- **Small Molecule**
- **Patent life 2038**
- **Inexpensive to manufacture**
- **Given by IV infusion, on the same day of the chemotherapy**
- **More than 500 Patient Data from Phase I,II,III**
- **Currently in Phase III**

These were phase 2 portions of Phase 2/3 Studies, and were designed as a multicenter, open label, randomized study.

Study BPI-2358-105

Phase 2/3, Multicenter, Randomized, Double Blind Study to Evaluate Duration of Severe Neutropenia with Plinabulin Versus Pegfilgrastimin Patients with Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy (Protective 1)

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)

Study BPI-2358-106

Phase 2/3, Multicenter, Randomized Study to Evaluate Plinabulin versus Pegfilgrastimin Reducing the Duration of Severe Neutropenia in Breast Cancer Patients Receiving Myelosuppressive Chemotherapy with Docetaxel, Doxorubicin, and Cyclophosphamide (TAC) (Protective 2)

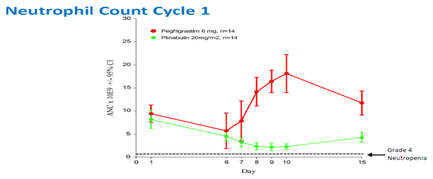
A total of N=72 BC patients were random with breast cancer assigned to the following combination arms:

Arm a: TAC + Pegfilgrastim (6 mg) (n=22)
Arm b: TAC + Pegfilgrastim (6 mg) + Plinabulin (20 mg/m2) (n=16)
Arm c: TAC +Pegfilgrastim (3 mg) + Plinabulin (20 mg/m2) (n=21)
Arm d: TAC+ Pegfilgrastim (1.5 mg) + Plinabulin (20 mg/m2) (n=14)

Target Patient Population:
Study 105: Patients with advanced or metastatic non-Small Cell Lung Cancer (NSCLC) after failing platinum-based therapy.
Study 106: Breast Cancer (BC) stage I,II,III patients who are candidate for adjuvant or neoadjuvant TAC

Plinabulin Versus Pegfilgrastim (Study 105)

Fig 1. Absolute Neutrophil Count in Cycle 1



	Baseline	D6	D7	D8	D9	D10	D15
Peg	9.436	5.717	7.853	14.169	16.410	18.122	11.740
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

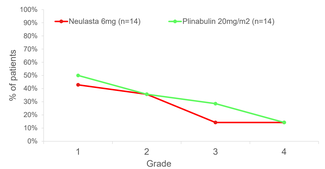
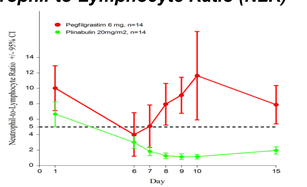
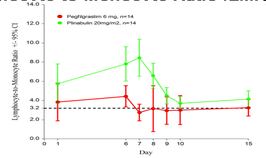


Fig 2. Neutrophil-to-Lymphocyte Ratio (NLR)



	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

Fig 3. Lymphocyte-to-Monocyte Ratio (LMR)



	Baseline	D6	D7	D8	D9	D10	D15
Peg	3.843	4.433	2.741	3.153	2.947	2.995	3.237
Plin 20mg/m2	5.747	7.812	8.453	6.591	4.502	3.701	4.154
P-value Peg vs. 20mg/m2	NS	0.0053	<0.0001	0.0527	NS	NS	NS

Plinabulin + Pegfilgrastim (Study 106)

Fig 4. Neutrophil-to-Lymphocyte Ratio (NLR)

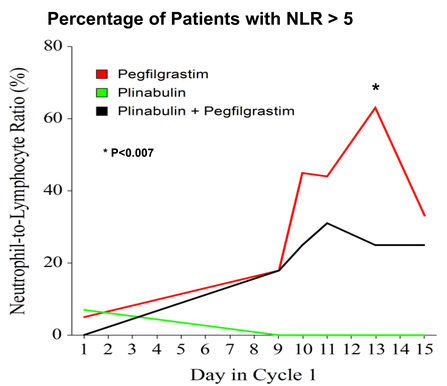
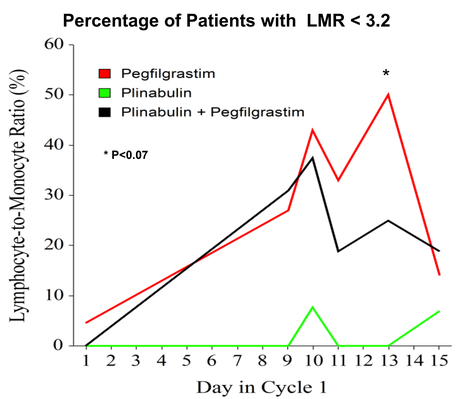


Fig 5. Lymphocyte-to Monocyte Ratio (LMR)



Plinabulin Summary

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

Conclusions

- **For Intermediate FN Risk (105 Study) Plinabulin is Equally effective as Pegfilgrastim for Chemo-Induced-Neutropenia (CIN)**
- **For High FN Risk (106 Study with TAC) Plinabulin plus Pegfilgrastim has better outcomes than either drug alone**
- **Pegfilgrastim, but not Plinabulin produces an Over-Production of Neutrophils leading to an Immune-Suppressive Phenotype:**
  - **NLR > 5**
  - **LMR < 3.2**

Adding Plinabulin to Pegfilgrastim leads to:

Reversal of the Immune-Suppressive Profile, by lowering the percentage of Patients with NLR < 5 or LMR > 3.2

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