Abstract #3590

A Randomized Phase 3 Clinical Trial of the Combination of Plinabulin (Plin) + Pegfilgrastim (Peg) Versus (vs) Peg Alone for TAC (docetaxel, doxorubicin, cyclophosphamide) Induced Neutropenia (CIN)

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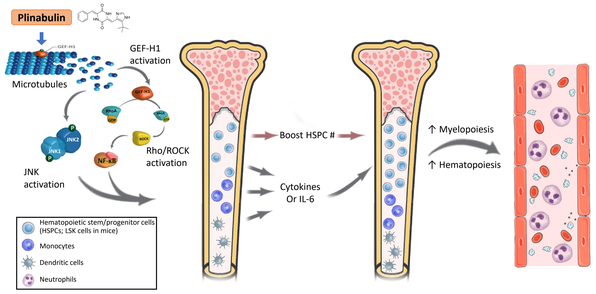
Background

- G-CSFs (including Pegfilgrastim) reduce, but do not completely ameliorate Chemotherapy-Induced Neutropenia (CIN).
- Plinabulin is a novel, small molecule, single-dose-per cycle therapy, with differentiated product profile versus Pegfilgrastim:
  - Plinabulin has equal Efficacy against single agent docetaxel CIN versus Pegfilgrastim
  - Plinabulin has less bone pain
  - Plinabulin, but not Pegfilgrastim protects against single agent docetaxel-induced thrombocytopenia
  - Plinabulin, but not Pegfilgrastim, has anticancer efficacy
- Plinabulin is dosed 30 minutes after chemotherapy, on the same day of chemotherapy
- Plinabulin has a different mechanism of action (MoA) than G-CSF
  - The absolute neutrophil count (ANC) nadir with Plinabulin occurs in week 2 and with Pegfilgrastim in week 1 after chemotherapy
  - Plinabulin induces
    - Neutrophil demargination and reduced neutrophil transit time from the bone marrow that is consistent with IL-6 signaling, and
    - Reversal of a LSK block in mouse bone marrow, suggest protective rather than a stimulatory MoA for Plin in CIN (Blayney, SLB 2018; Ghosh, AACR 2018, Suwa, Am J Physiol 2000).
- Due to their differences in MoA, there is a strong rationale to combine Plinabulin and Pegfilgrastim, as this offers the potential of better protection against CIN in both week 1 and 2 in the chemo cycle.
- In the Phase II portion of study BPI2358-106 (Study 106), we evaluated the effects of the Plinabulin combined with Pegfilgrastim on CIN and Bone Pain.

MoA - Plinabulin - first-in-class agent with GEF-H1 as new target



Method

Study 106 Phase 2 treated breast cancer (BC) patients with TAC (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 600 mg/m^2) and:

- 6 mg Pegfilgrastim alone (Peg6) (n=22)
- Pegfilgrastim 6 mg + Plinabulin 20 mg/m^2 (n=16)
- Pegfilgrastim 3 mg + Plinabulin 20 mg/m^2 (n=21)
- Pegfilgrastim 1.5 mg + Plinabulin 20 mg/m^2 (n=14)

Endpoints:

- ANC nadir
- Grade 3/4 Neutropenia frequency & Grade 4 Neutropenia frequency
- Duration of Grade 3/4 Neutropenia (DSN) Mean +/-SD & Median
- Bone pain
- Neutrophil Count was obtained on days 0, 1, 3, 6, 7, 8, 9, 10, 11, 12, 13, 15 of Cycle 1.
- Bone Pain was assessed by a validated questionnaire on days 1, 2, 3, 4, 6, 7, 8, 9, and expressed as % of patients reporting bone pain.

106 Phase 2 Results

Figure 1: Time Course of Absolute Neutrophil Count (Median, ANC Log-Scale)

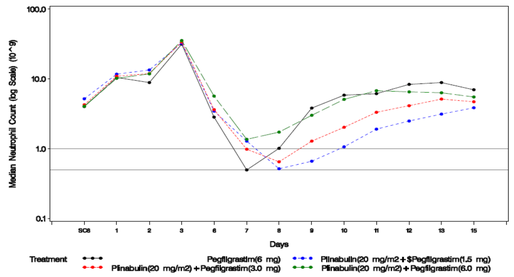


Figure 2: Grade 3/4 Neutropenia Frequency (%)

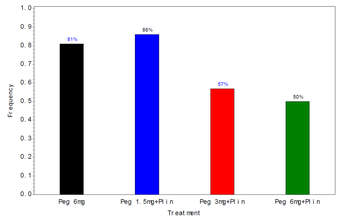


Figure 3: Grade 4 Neutropenia Frequency (%)

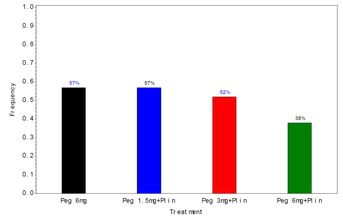


Figure 4: Nadir (Mean +/- SD)
Absolute Neutrophil Count (Cellsx10E9/L)

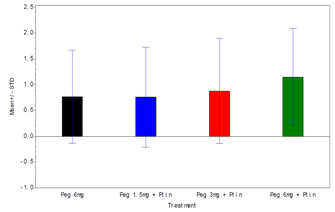


Figure 5: DSN (Median) (Days)

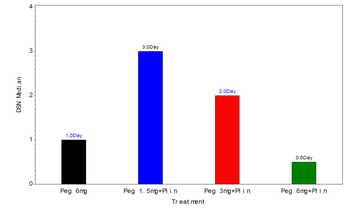
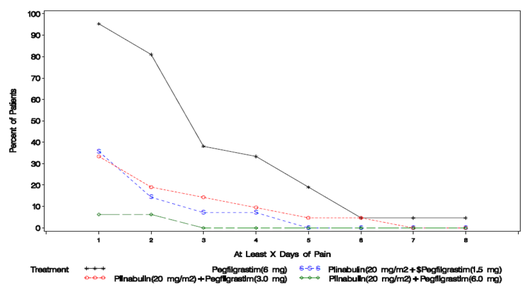


Figure 6: Time Course of Bone Pain



Summary Table	Pegfilgrastim 6mg N=21	Pegfilgrastim 6mg + Plinabulin 20 mg/m^2 N=16
Gr 3/4 Neutropenia %	81%	50% (P value < 0.05)
Gr 4 Neutropenia %	57%	38%
DSMN mean (±SD)	1.4 (±1) day	0.9 (±1.1) day
DSMN median	1 day	0.5 day
Nadir mean (±SD)	0.77 (±0.90) μ/L	1.15 (±0.94) μ/L
Bone Pain ≥ 1 day	95%	6% (P value < 0.001)
Bone Pain ≥ 4 days	33%	0% (P value < 0.01)
Immune Suppression	Yes	Limited
Anti-cancer	No	Yes

106 Phase 3 Design: Superiority Trial

Key Enrollment Criteria:

- Candidates for adjuvant or neoadjuvant TAC that are in Early stage (Stage I and II) and Stage III Breast Cancer or have had no prior chemotherapy.
- No history of myelogenous leukemia, myelodysplastic syndrome, or sickle cell disease.
- No chronic use of Filgrastim, Pegfilgrastim, or any bioequivalent (biosimilar) for severe chronic neutropenia or other chronic neutropenia syndrome

Methods

- Neutrophil Count obtained on days 0, 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13, 15 of Cycle 1.
- Bone Pain assessed by a validated questionnaire on pre-dose Day -1 to Day 10 and expressed as % of patients reporting bone pain.

Endpoint:

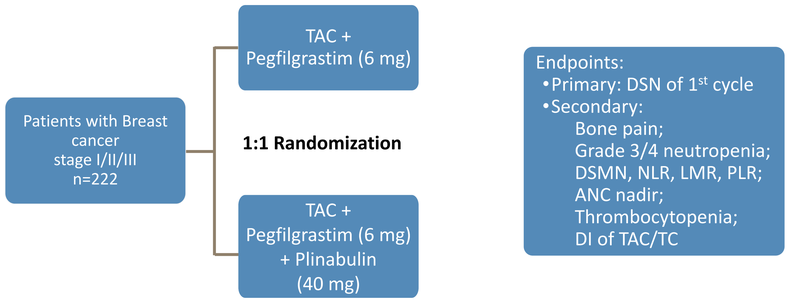
- DSN in 1st Cycle
- Maximum daily bone pain intensity from Day -1 to 10
- Portion of patients with Grade 3 or 4 neutropenia
- DMSN of 1st Cycle
- NLR, LMR, PLR
- ANC nadir
- Thrombocytopenia
- Changes in dose intensity (DI) of TAC/TC

AIM:

To Demonstrate Superiority of the Plinabulin/Pegfilgrastim combination vs Pegfilgrastim monotherapy for:

- DSN
- Bone Pain

Study 106 Phase 3
40-50% Western Patient Population; Double Blinded



Study 106 Phase 3 Current Status

Randomized: 17 pts (Target: 222 pts)
Countries: China; US; Ukraine
Expected first interim analysis: March 2020

Conclusion

➢**This confirmatory Phase 3 portion of Study 106 will evaluate Superiority of the combination of Plinabulin and standard dose Pegfilgrastim 6mg, for TAC CIN vs Pegfilgrastim alone.**

➢**The Plinabulin/Pegfilgrastim combination is a novel CIN approach with the potential to optimize chemotherapy, by minimizing chemotherapy dose modifications due to CIN or Bone Pain.**

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