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
- 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/m², doxorubicin 50 mg/m², cyclophosphamide 600 mg/m²) and:
- 6 mg Pegfilgrastim alone (Peg6) (n=22)
- Pegfilgrastim 6 mg + Plinabulin 20 mg/m² (n=16)
- Pegfilgrastim 3 mg + Plinabulin 20 mg/m² (n=21)
- Pegfilgrastim 1.5 mg + Plinabulin 20 mg/m² (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

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.

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

Endpoints:
- Primary: DSN of 1st cycle
- Secondary: Bone pain; Grade 3/4 neutropenia; DSmN, NLR, LMR, PLR; ANC nadir; Thrombocytopenia; DI of TAC/TC

AIM: Superiority of the combination of Plinabulin and standard dose Pegfilgrastim 6mg, for TAC CIN vs Pegfilgrastim alone.

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 andstandard 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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