Abstract #91348

Plinabulin, a Novel Small Molecule That Ameliorates Chemotherapy-Induced Neutropenia, Is Administered on the Same Day of Chemotherapy and Has Anticancer Efficacy

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Background

Plinabulin is a novel small molecule with immune-enhancing effects and anti-cancer activity. Plinabulin induces dendritic cell maturation and their production of interleukin-1β (IL-1β), IL-6, and IL-12 (Lloyd et al, 2016), all of which are important in maintaining neutrophil survival.

Phase 1 and 2 solid tumor trials of plinabulin in >140 patients with routine safety laboratory assessments, revealed a protective effect against chemotherapy-induced neutropenia.

In preclinical studies, plinabulin was protective against docetaxel- or cyclophosphamide-induced neutropenia via a mechanism of action different from that of granulocyte colony-stimulating factor (G-CSF) analogues.

Currently, G-CSF and its analogues are standard of care for the prevention of chemotherapy-induced neutropenia. G-CSFs have important limitations:

- **Concurrent chemotherapy and G-CSFs administration is contraindicated, as:**
  - **G-CSF is not protective against febrile neutropenia**
  - **G-CSF may worsen neutropenia**
- **Due to its bone-marrow-stimulating mechanism of action, G-CSF causes bone pain in ~30% of patients, limiting its use**
- **G-CSF and its biosimilars are expensive-to-make biologics**

Materials & Methods

In the phase 1 trial, plinabulin was given as monotherapy in a dose range of 2 mg/m2 to 30 mg/m2 in 38 oncology patients, with the objective to assess safety, tolerability and the determination of RP2D. Plinabulin doses were administered on day 1,8 and 15 of each 4 week cycle. Routine safety assessments, including Neutrophil Counts were determined. In the phase 2 clinical trial, patients were randomized to receive docetaxel 75 mg/m^2 alone (n=73) or docetaxel 75 mg/m^2 followed by plinabulin at 30 mg/m^2 (n=50) or at 20 mg/m^2 (n=40) on day 1 and day 8 of each 3-week cycle (clinicaltrials.gov NCT00630110). Plinabulin was given by a 30-minute intravenous (IV) infusion, starting 1 hour after administration of docetaxel. Since this was an anti-cancer trial, the primary efficacy endpoint was median overall survival. Secondary endpoints included safety assessments, such as complete blood count measurements that included neutrophil counts, on Days 1, 8, and 15 of each cycle.

Results

Fig. 1 **Phase 1 monotherapy data with Plinabulin:**

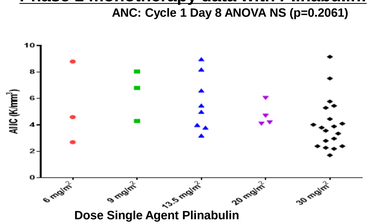

Figure 1– Neutrophil counts on Day 8 of Cycle 1 of Plinabulin monotherapy. ANC was not increased

Fig. 2 **Phase 2 combination therapy with Docetaxel+/- Plinabulin:**

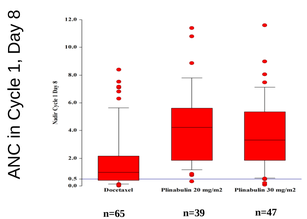

Figure 2 -- Neutrophil counts on day 8 of Cycle 1. Plinabulin 20 mg/m^2 or 30 mg/m^2 largely prevented Docetaxel-induced reduction in neutrophil count. [Day 8 is the neutrophil nadir after Day 1 Docetaxel administration (Blackwell Ann Oncol 2015)]

Docetaxel vs. Plinabulin 20 mg/m^2 + Docetaxel ; p- < 0.0001
Docetaxel vs. Plinabulin 30 mg/m^2 + Docetaxel ; p-< 0.0001
Plinabulin 20 mg/m^2 vs. Plinabulin 30 mg/m^2 ; p = 0.41

Fig. 3

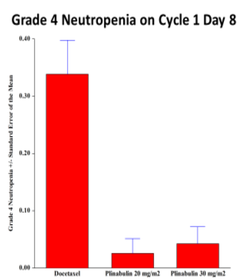

Figure 3 -- Proportion of patients with Cycle 1, Day 8 grade 4 neutropenia is reduced by addition of Plinabulin to Docetaxel from 33.3% to 4.6% (p<0.0003)

(Grade 4 neutropenia = absolute neutrophil count [ANC] <0.5x10^9/L)

Docetaxel vs Plinabulin 20 mg/m^2 + Docetaxel: p = 0.00026
Docetaxel vs Plinabulin 30 mg/m^2 + Docetaxel : p = 0.00018
Plinabulin 20 mg/m^2 vs Plinabulin 30 mg/m^2 : p = 0.68

Fig.4

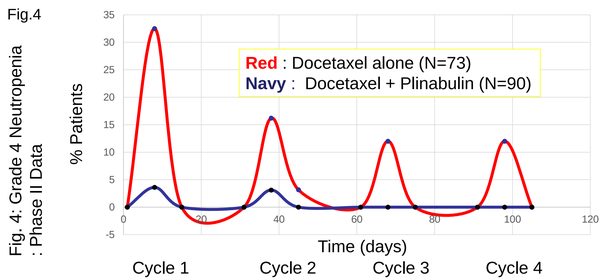

Figure 4 -- Frequency of grade 4 neutropenia over cycles 1,2,3,4 with Docetaxel with and without Plinabulin

Plinabulin also reduced the clinical sequelae associated with docetaxel-induced neutropenia (sepsis, infections, hospitalizations, need for docetaxel dose reduction, and G-CSF use). Bone pain was 4% in patients receiving plinabulin. Plinabulin had a favorable safety profile; grade 3 transient hypertension in 20% and 5% of patients receiving 30 mg/m^2 and 20 mg/m^2 plinabulin, respectively,was the most frequently reported finding.

Discussion

Plinabulin has demonstrated preliminary efficacy in patients with advanced non-small cell lung cancer (NSCLC) in a phase 2 study (clinicaltrials.gov NCT00630110) A Phase 3 global trial of second- or third-line chemotherapy with docetaxel + plinabulin compared to docetaxel + placebo in patients with advanced NSCLC with at least one measurable lung lesion is underway (clinicaltrials.gov NCT02504489). In addition, plinabulin is being developed for the mitigation of chemotherapy-induced neutropenia. Administered by IV infusion on the same day of chemotherapy, plinabulin will be given in a single dose of 20 mg/m^2 per cycle. The mechanism of action of plinabulin is different from that of G-CSF. In contrast to G-CSF, plinabulin does not promote neutrophil cell production in the absence of chemotherapy. Plinabulin's site of action does not appear to be the bone marrow, given that bone pain rarely occurred with plinabulin. Plinabulin's protective effects against docetaxel-induced neutropenia are proposed to be via an immune mechanism. Plinabulin is expected to be more effective than G-CSF in the prevention of chemotherapy-induced neutropenia. Plinabulin is effective against chemo agents other than docetaxel; i.e. cyclophosphamide. A global phase 2/3 program for the concurrent administration with a myelosuppressive chemotherapeutic regimen for the prevention of chemotherapy induced neutropenia has been initiated.

Conclusions

Plinabulin, a small molecule given by IV infusion, has the potential to be an effective, safe (with much less bone pain), cost effective, and convenient (same day dosing vs next day dosing for G-CSF) alternative to G-CSF for the prevention of chemotherapy-induced neutropenia. Plinabulin has a favorable Target Product Profile (See Table)

Plinabulin Target Product Profile

	Plinabulin Better Than G-CSF
Efficacy	✔
Safety	✔
Same Day Dosing	✔
Cost-Effectiveness	✔

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