



# PLINABULIN RAPIDLY (WITHIN 24 HOURS) REVERSES MYELOSUPPRESSION INDUCED BY CHEMOTHERAPY

Abstract 2056

Authors, D.W. Blayney<sup>1</sup>, M. Chang<sup>2</sup>, L. Huang<sup>2</sup>, and R. Mohanlal<sup>2</sup>

1. Stanford Cancer Institute, Stanford, CA  
2. BeyondSpring Pharmaceuticals, Inc New York, NY

## INTRODUCTION

- In PROTECTIVE-2 (BPI-2358-106; NCT03294577), Plinabulin (Plin)+Pegfilgrastim (Peg) was superior to Peg for the prevention of chemotherapy-induced neutropenia<sup>1</sup>
- Grade 4 neutropenia was 86% in the Peg arm and 68% in the Plin+Peg arm ( $P < 0.0015$ )<sup>2</sup>
- Plin has a fast onset of activity in the first week of the chemotherapy (chemo) cycle, Peg activity has a slower onset in the second week<sup>3</sup>

## AIM

To further evaluate Plinabulin's fast onset mechanism of action (MoA) and a potential progenitor stem cell involvement in Plinabulin's fast onset MoA

## METHODS

### Patients and treatments

- In both PROTECTIVE-1 and PROTECTIVE-2, patients were randomized to either Plin/Plin plus Peg or Peg<sup>1,4</sup>
- Patients in the Plin arms received Plin (30-minutes intravenous (IV) infusion, 30 minutes after chemo) on Day 1 of the first 21-day cycle
- Plin doses were 5, 10, or 20 mg/m<sup>2</sup>, or a 40-mg fixed dose (equivalent to 20 mg/m<sup>2</sup> (PROTECTIVE-1)<sup>3</sup> or 10, 20, or 30 mg/m<sup>2</sup>, or a 40-mg fixed dose (PROTECTIVE-2)<sup>1,5</sup>
- Patients in the Peg arms received 6 mg Peg 24 hours after chemo, on Day 2
- The Peg arm is the no-treatment control for the Plin arm, as blood was drawn before the Peg dose was administered on Day 2 and patients received 0 mg/m<sup>2</sup> Plin in this arm
- Patients in the Peg arm did not receive any Peg before their blood was collected for this analysis

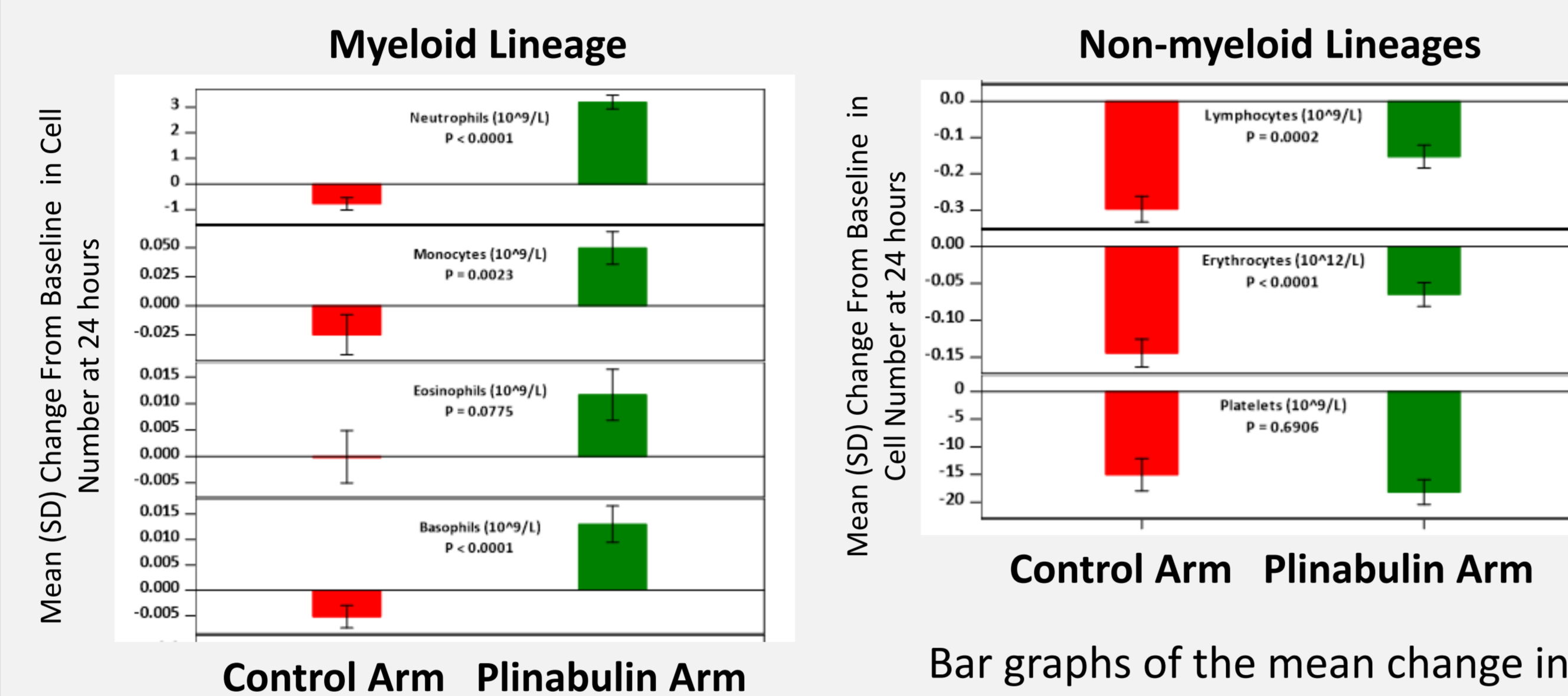
### Analyses

- Absolute neutrophil (N) count (ANC) and counts of monocytes (M), eosinophils (E), basophils (B), lymphocytes (L), erythrocytes (RBC), and platelets (P) were obtained from peripheral blood draws and analyzed by a central laboratory
- The primary analysis was to compare cell counts at 24 hours post-chemo on cycle (C) 1 day (D) 2 between patients treated with 20 mg/m<sup>2</sup> or a 40-mg fixed dose Plin and patients in the control arm
- Cell counts on C1D2 were expressed as change from pre-dose C1D1, in absolute values
- A secondary analysis was to find correlation coefficients ( $r$ ; Pearson linear regressions of scatter plots) between counts of N and those of M, E, B, L, RBC, and P on C1D2 among all patients in the Plin arm (5, 10, 20, 30 mg/m<sup>2</sup>, 40 mg fixed) and patients in the Control arm (Plin 0 mg/m<sup>2</sup>) (total=451).

## RESULTS

### Plinabulin mitigates pan-myelosuppression of docetaxel and TAC in most blood cell types

The graphs show changes at 24 hours post-chemo with or without Plinabulin



### Mean (SD) Cell Number at Baseline (C1D1)

Cell type, 10 <sup>9</sup> cells/L <sup>a</sup>	Plinabulin (0 mg/m <sup>2</sup> ), mean (SD) (n=172) <sup>b</sup>	Plinabulin (20 mg/m <sup>2</sup> or 40 mg), mean (SD) (n=228) <sup>c</sup>	P value
Basophils	0.03 (0.03)	0.03 (0.03)	0.40
Eosinophils	0.07 (0.06)	0.07 (0.06)	0.62
Erythrocytes	4.37 (0.43)	4.35 (0.39)	0.35
Lymphocytes	1.12 (0.54)	1.15 (0.57)	0.47
Monocytes	0.32 (0.24)	0.27 (0.17)	0.19
Neutrophils	10.07 (4.51)	9.97 (4.10)	0.96
Platelets	284.93 (81.51)	273.08 (64.10)	0.21

<sup>a</sup> Erythrocytes are reported as 10<sup>12</sup> cells/L. <sup>b</sup> n=169 for platelets. <sup>c</sup> n=219 for platelets.  
Docetaxel 75 mg/m<sup>2</sup> Day1; SD, standard deviation; TAC, docetaxel 75 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup> Day1

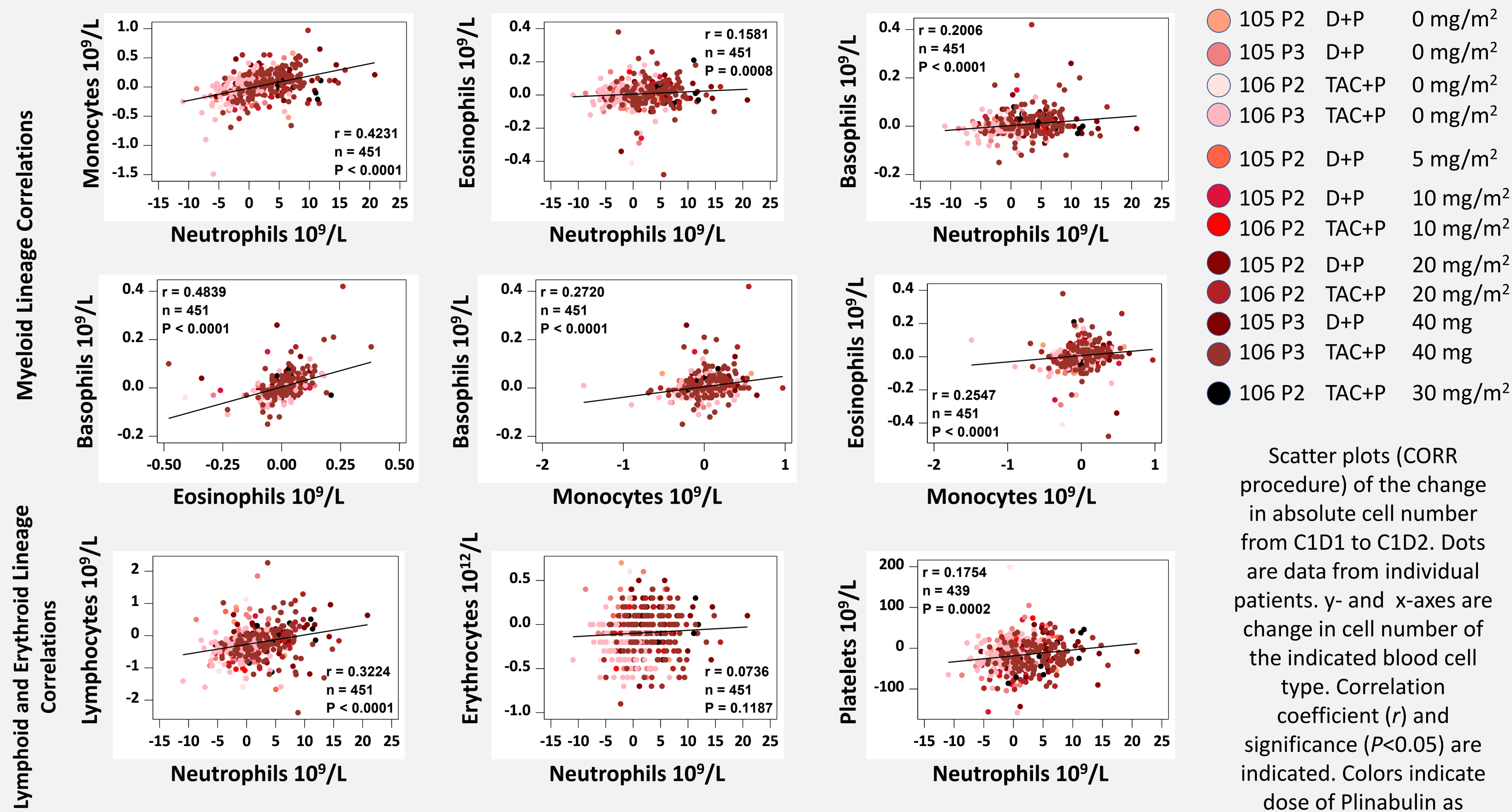
Bar graphs of the mean change in cell number from C1D1 to C1D2 (y-axes) for each blood cell type as shown (x-axes). Red, Control arm (0 mg/m<sup>2</sup> Plinabulin); Green, Plinabulin arm. Error bars show the standard deviation (SD). Significance  $P < 0.05$ . n=172 for Control for all cell types but platelets (n=169); n=228 for Plinabulin 20mg/m<sup>2</sup> and 40 mg fixed dose for all cell types but platelets (n=219).

## CONCLUSIONS

- Plinabulin rapidly (within 24 hours) reversed chemo-induced myelosuppression
- Adding Plinabulin to a myelosuppressive regimen reversed the loss of neutrophils and other white blood cell types of the myeloid lineage
- Plinabulin significantly reduced the loss of lymphocytes and erythrocytes, but not platelets
- The data suggest that Plinabulin is active in granulocyte-monocyte-progenitor (GMP) stem cells (N, M, B and E progenitor) as well as progenitor cells further upstream in the hematopoietic lineage
- Our findings are supported by pre-clinical data showing that Plinabulin protects murine Lin-Sca1+c-Kit+ (LSK) hematopoietic cells, the equivalent of human CD34+ cells<sup>6,7</sup>

### Plinabulin-mediated increases in cell numbers are dose-dependent and correlated among cells of the myeloid, lymphoid, and erythroid lineages

The scatterplots show changes at 24 hours post-chemo with or without Plinabulin



D, docetaxel 75 mg/m<sup>2</sup> Day1; P2, phase 2; P3, phase 3; P, plinabulin; TAC, docetaxel 75 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup> Day1. n=172 for Control for all cell types but platelets (n=169); n=279 for Plinabulin 5, 10, 20, and 30 mg/m<sup>2</sup> and 40 mg fixed dose for all cell types but platelets (n=270).

- 105 P2 D+P 0 mg/m<sup>2</sup>
- 105 P3 D+P 0 mg/m<sup>2</sup>
- 106 P2 TAC+P 0 mg/m<sup>2</sup>
- 106 P3 TAC+P 0 mg/m<sup>2</sup>
- 105 P2 D+P 5 mg/m<sup>2</sup>
- 105 P2 D+P 10 mg/m<sup>2</sup>
- 106 P2 TAC+P 10 mg/m<sup>2</sup>
- 105 P2 D+P 20 mg/m<sup>2</sup>
- 106 P2 TAC+P 20 mg/m<sup>2</sup>
- 105 P3 D+P 40 mg
- 106 P3 TAC+P 40 mg
- 106 P2 TAC+P 30 mg/m<sup>2</sup>

Scatter plots (CORR procedure) of the change in absolute cell number from C1D1 to C1D2. Dots are data from individual patients. y- and x-axes are change in cell number of the indicated blood cell type. Correlation coefficient ( $r$ ) and significance ( $P < 0.05$ ) are indicated. Colors indicate dose of Plinabulin as above.

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## CONTACT INFORMATION

Douglas W. Blayney, MD  
[DBlayney@stanford.edu](mailto:DBlayney@stanford.edu)  
Ramon Mohanlal, MD, PhD  
[RMohanlal@beyondspringpharma.com](mailto:RMohanlal@beyondspringpharma.com)