PLINABULIN IS A SMALL MOLECULE CLINICAL STAGE IMMUNE-ONCOLOGY AGENT FOR NSCLC

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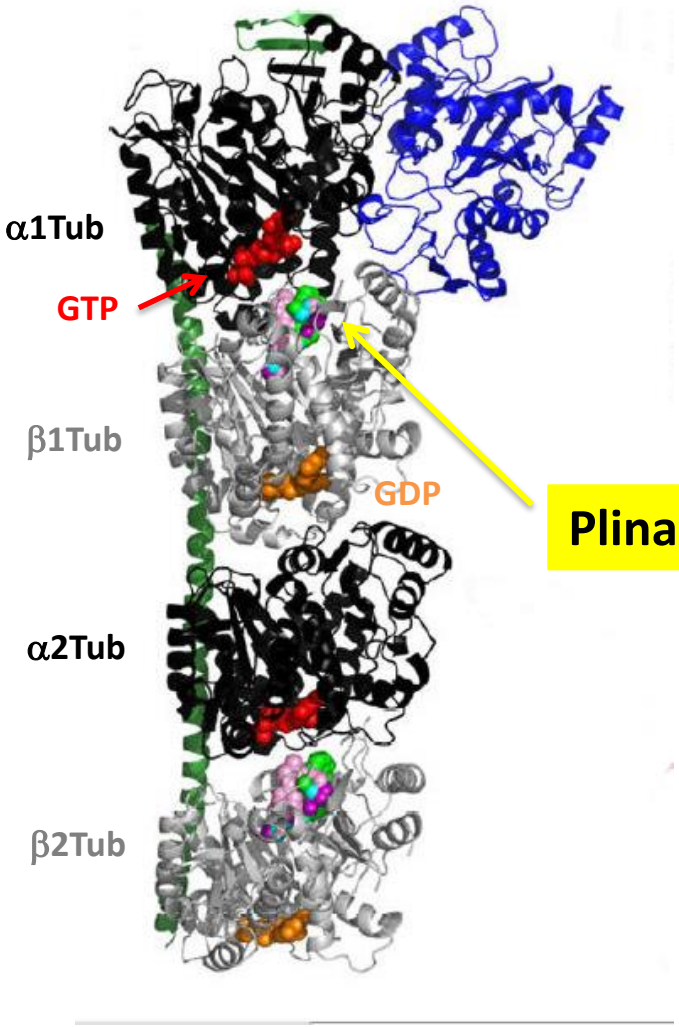
BeyondSpring

Transformational Science Advancing Oncology

Plinabulin's Target is Tubulin in Microtubules

Cell Cytoskeleton Consists of Polymerized Tubulin



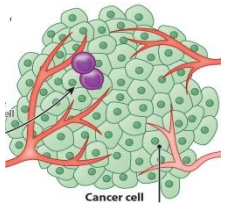
Plinabulin

- **Immune – Related Anticancer Effects**
- **Neutrophil Rescue Effects**
- **Vascular Disruptive Effects**

Wang Y et al. FEBS J. 2016; 283: 102-111
Singh AV et al. Blood 2011l 117: 5692-5700

Plinabulin Anti-Cancer MOA: Immune-Enhancing and Apoptosis

Cancer Cells



Tumor Antigen

MHCII

Tumor Killing

Apoptosis
Caspase-3
Activation

Plinabulin

RhoB

Dendritic Cell

Tubulin ▸ ▸ ▸ ▸ JNK Activation ▸ C-Jun ▸ ▸ ▸ ▸

CD80
CD86

Co-Stimulation

T-Cell Activation

T-Cell

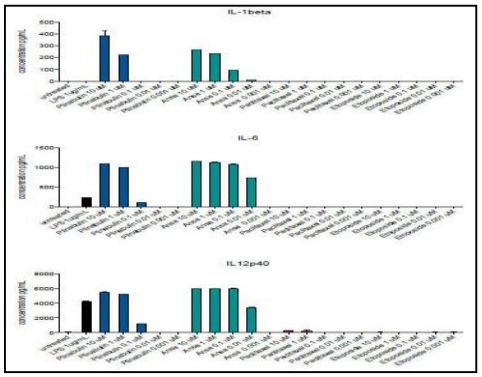
Heasman et al. Coordinated RhoA signaling at the leading edge and uropod is required for T cell transendothelial migration. J cell Biol. 190: 553-563 (2010).

Plinabulin MOA for Neutrophil Protection

IL-1β

IL-6

IL-12



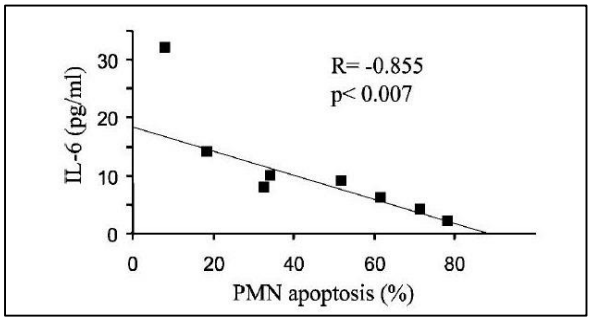
Plinabulin → **Dendritic Cell**: Tubulin ▸ ▸ ▸ ▸ JNK-Activation ▸ C-Jun ▸ ▸ ▸

IL-6
IL-12

Apoptosis Prevention

Shear stress-induced neutrophil migration *

Neutrophil



*Fine et al. GEF-H1 is necessary for neutrophil shear stress-induced migration during inflammation, JCB 215(1): 107-119 (2016)

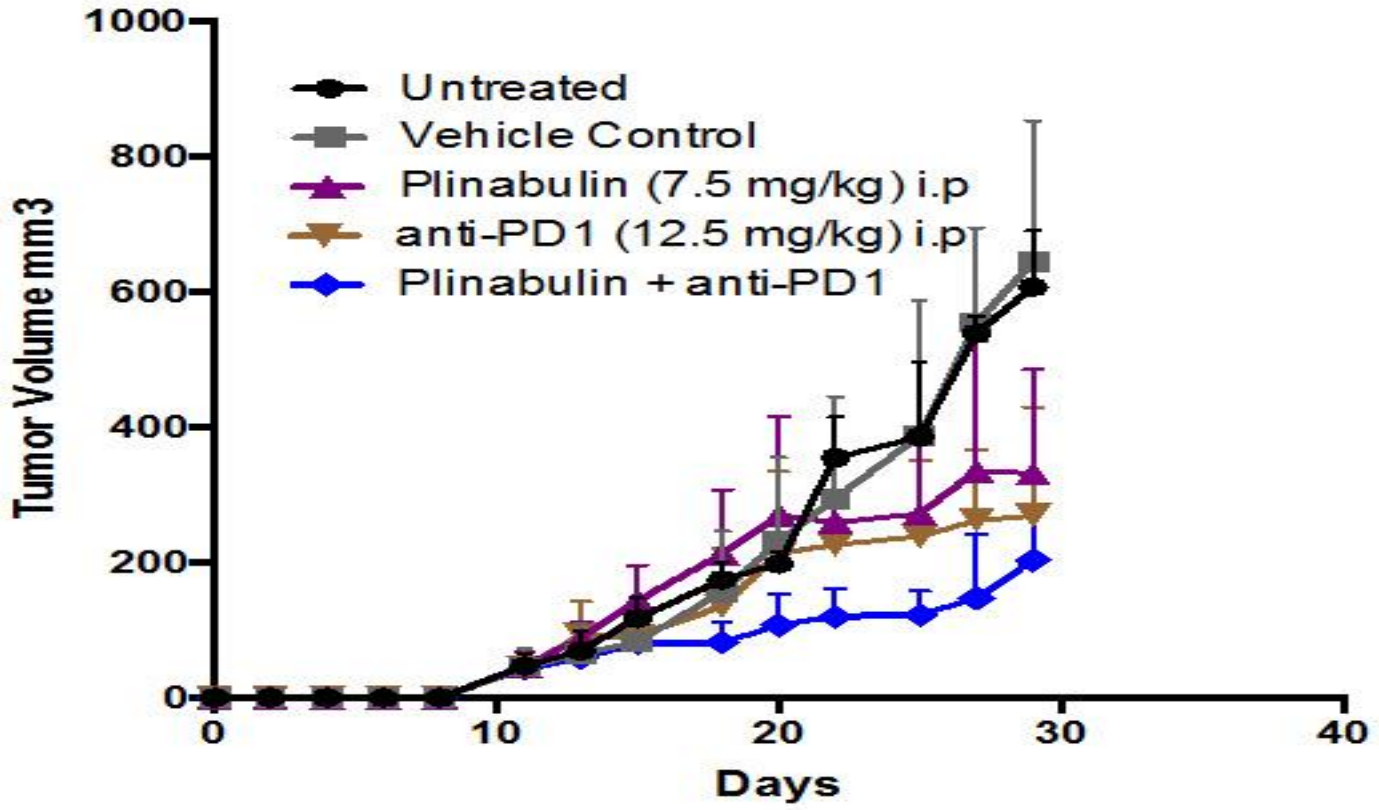
Plinabulin: Immune-Oncology Effects

- Induces Maturation of Dendritic Cells (DCs)
  - ↑Phenotypic Cell Surface Markers:
    - CD-40, CD-80, CD-86, MHCII
- Release of Neutrophil-Protective Cytokines
    - IL-1β, IL-6, IL-12
- Synergistic Antitumor Effects in Combination with PD1- and CTLA4- inhibitor in Tumor Models
    - MC-38 Colon Tumor, TS/A Breast Tumor Model
      - ↑CD4 T-cell proliferation
      - ↓Regulatory T-cells
      - ↓ M2 macrophages

Plinabulin + Nivolumab Breast Cancer Animal Model

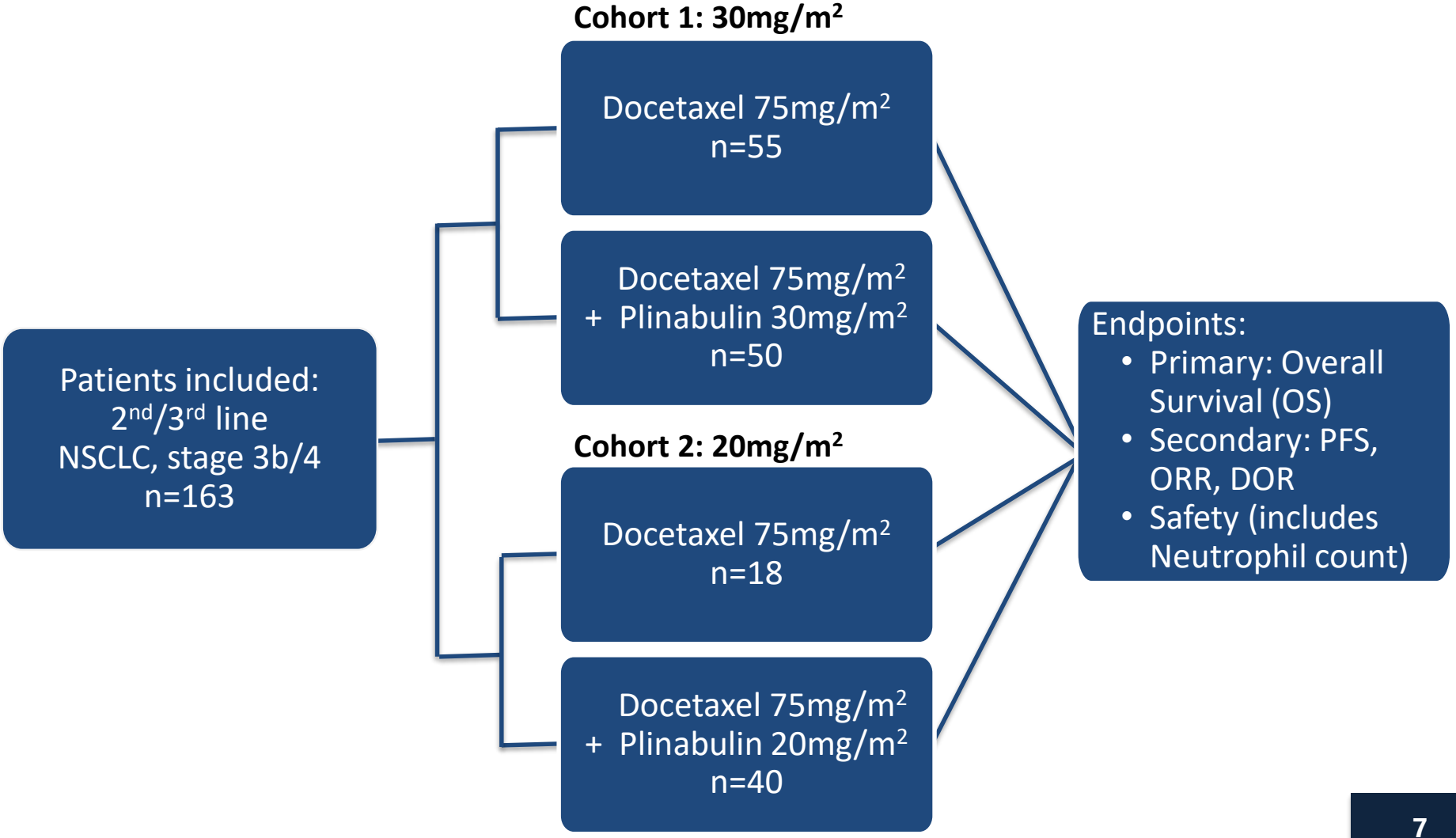
Improved Anti-Cancer Efficacy when Plinabulin is Combined with:

- **PD1-Inhibitor**
- **PD1-Inhibitor +CTLA-4 Inhibitor**



- Dr. Zippelius Lab at Univ. of Basel

Plinabulin + Docetaxel in NSCLC: Phase 2 Trial Design



Plinabulin: NSCLC Phase 2 Efficacy Summary

ITT Patient Population

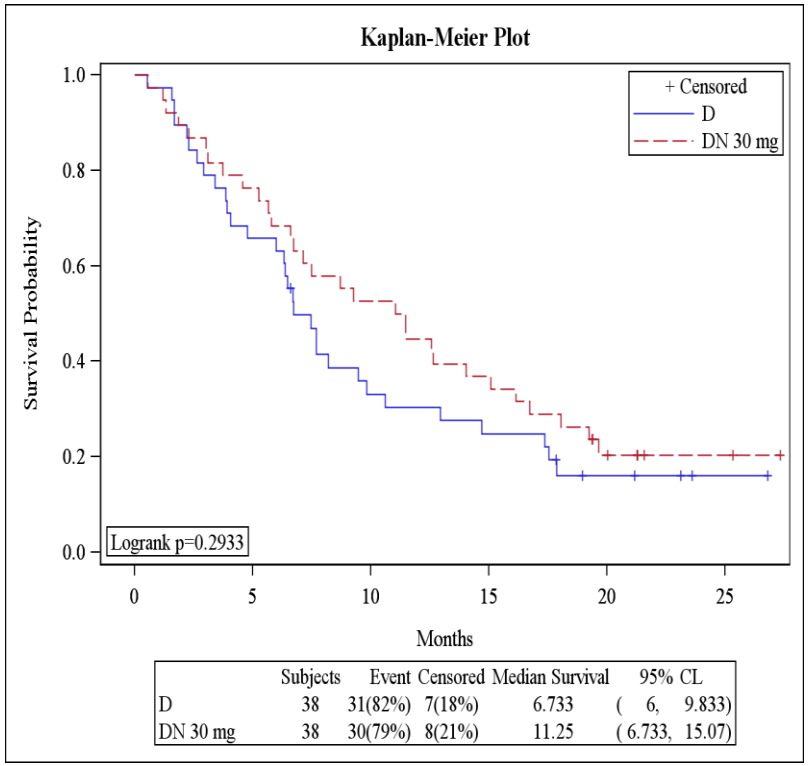
Endpoints	Plinabulin + Docetaxel (DN) (D) 75mg/m^2 + (N) 30 mg/m^2	Docetaxel alone (D) 75mg/m^2
	N=50	N=55
Median OS, Months (90% CI)	8.7 (6.6,12.6)	7.5 (6.3, 10.5)
Median Duration of Response (DOR)* Months (90% CI)	**12.7 (4.0, 13.9)**	**1.5 (1.1, 3.1)**

*** p<0.05 Plinabulin + Docetaxel vs Docetaxel alone**

Phase 2 Study of Docetaxel +/- Plinabulin in NSCLC

Encouraging Activity in Measurable Lung Lesion

Durable Response and Extended Survival Benefit of 4.6 Month



	Plinabulin + Docetaxel (DN)	Docetaxel alone (D)
	N=38	N=38
mOS	11.3 M	6.7 M
	P = 0.29	
DOR	12.7 M	1.0 M
	P<0.05	
ORR	18.4%	10.5%
PFS	3.7 M	2.9 M

Plinabulin: NSCLC Phase 2 Safety Summary

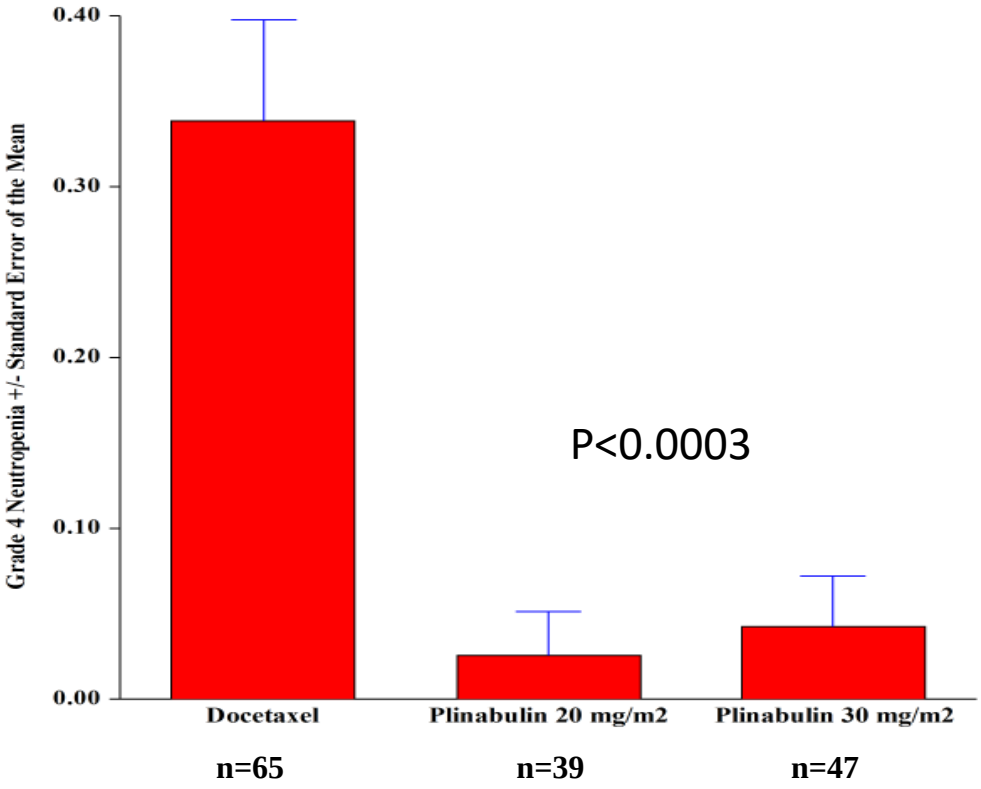
Common (>=20%) AEs (% Grade 1-4;% Grade 3-4)

	30 D (n=55)	30 DP (n=50)	20 D (n=18)	20 DP (n=40)
Nausea	44;0	48;4	22;0	40;0
Fatigue	40;11	52;4	39;6	30;3
Diarrhea	33;4	58;8	33;11	35;5
Constipation	33;0	36;0	17;6	28;0
Anorexia	31;0	34;0	39;0	25;3
Pyrexia	29;2	30;0	17;0	23;0
Vomiting	22;0	34;4	33;6	35;0
Cough	33;0	22;0	28;0	33;0
Alopecia	29;0	28;0	44;0	25;0
Dyspnea	24;13	22;4	28;17	28;5
Neutropenia	**36;27**	**8;8**	**22;22**	**8;5**
Myalgia	22;0	22;2	11;0	8;0
Anemia	16;2	24;8	17;0	20;5
Asthenia	**26;4**	**8;2**	**28;6**	**20;13**
Headache	9;0	22;0	17;0	26;3
Dizziness	6;0	22;0	17;0	5;0
Hypokalemia	2;1	20;0	11;0	5;5
Leukopenia	9;5	6;2	22;22	7;0
Tachycardia	4;0	14;0	22;0	5;0
Arthralgia	11;0	14;0	22;0	15;0
Transient Hypertension	**4;0**	**32;20**	**6;0**	**23;5**

Phase 2 Data: Grade 4 Neutropenia in Cycle 1 Day 8

Plinabulin ITT Population

Proportion of Patients with Grade 4 Neutropenia



Docetaxel Alone **Docetaxel + Plinabulin**

Adverse events	Plinabulin + Docetaxel (n=90)	Docetaxel (n=73)
Sepsis	0 %	3.6 %
Severe infections	0 %	3.6 %
Docetaxel dose reduction due to toxicity	6.7 %	19.2 %

CONCLUSIONS (1)

- **Phase 2 Data Plinabulin/Docetaxel vs Docetaxel alone:**
  - **mOS benefit of 4.6 months in pts with a measurable lung lesions**
  - **Prolonged DOR**
  - **Prevention of Grade 4 Neutropenia**
  - **No increase in immune-related AEs vs Docetaxel alone**
- **A Global Phase 3 Study in NSCLC Patients with a Measurable Lung Lesion has been Initiated Globally**

A Randomized, Single-Blinded, Phase 3 Study of Second- or Third-Line Chemotherapy with Docetaxel + Plinabulin Compared to Docetaxel + Placebo in Patients with Advanced Non-Small Cell Lung Cancer with at Least One Measurable Lung Lesion *(DUBLIN-3)*

CONCLUSIONS (2)

- **Plinabulin Has Potent Immune-Enhancing Effects**
  - **Preclinical Evidence**
  - **Clinical Evidence**
- **Two IIT Phase 1/2 Trials Plinabulin/Nivolumab Combination Trials have been Initiated in NSCLC**

UCSD Phase 1/2 Trial Design:

- 28 days per cycle
- Plinabulin (IV): Day 1, 8, 15
- Nivolumab (IV): Day 1, 15

Fred Hutchinson Phase 1/2 Trial Design:

- 28 days per cycle
- Plinabulin (IV): Day 1, 15
- Nivolumab (IV): Day 1, 15

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Less Grade 3 Respiratory Symptoms with Plinabulin

Baseline	Docetaxel Monotherapy (n=38)	Docetaxel + Plinabulin 30 mg/m2 (n=38)
Patients (%) with Respiratory Symptoms	65.8%	73.7%