BeyondSpring

Plinabulin R&D Day

June 25, 2021 | NASDAQ: BYSI

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By attending this presentation, you acknowledge that you will be solely responsible for your own assessment of the market and our market position and that you will conduct your own analysis and be solely responsible for forming your own view of the potential future performance of our business.

Agenda

1.	**Introduction**	Dr. Lan Huang, CEO
2.	**Overview Triple IO Strategy with Plinabulin**	Dr. Ramon Mohanlal, CMO, EVP R&D
3.	**Plinabulin + Nivolumab + Ipilimumab**	Dr. Ramon Mohanlal, CMO, EVP R&D
4.	**Plinabulin + Radiotherapy + PD1/PD-L1-inhibitor**	Dr. Steven Lin, MD Anderson
5.	**DUBLIN-3**	Dr. Trevor Feinstein, Piedmont Cancer Institute
6.	**Financial update**	Elizabeth Czerepak
7.	**Q&A**	

Leading Expert Speakers Biographies

Dr. Steven Lin

Dr. Steven Lin is an Associate Professor and Physician Scientist at MD Anderson Cancer Center, with joint appointments in the Departments of Radiation Oncology and Experimental Radiation Oncology. Dr. Lin's practice focuses on thoracic malignancies, and he oversees several clinical trials including the use of proton beam therapy for esophageal cancer and in the combination of immunotherapy with radiotherapy in lung and esophageal cancers. Dr. Lin runs a translational research team that evaluates biomarkers for treatment response and disease outcomes after chemoradiation therapy and immunotherapy. On the basic science side, Dr. Lin's main interests lie in identifying novel approaches that could enhance radiotherapy and immunotherapy combinations in lung cancer that could be translated to innovative clinical trials for patients.

Dr. Trevor Feinstein

Dr. Trevor Feinstein is board certified in medical oncology and hematology by the American Board of Internal Medicine. Dr. Feinstein graduated from University of Illinois medical school and completed his residence and fellowships at the University of Pittsburgh. He joined Piedmont Cancer Institute in 2011. He is a certified member of MD Anderson Cancer Network. He is a co-investigator on several peer-reviewed research projects and actively involved in clinical trials focusing on improved therapies for various cancers. He is director of research at Piedmont Fayette Hospital. Dr. Feinstein has authored numerous publications and abstracts in Hematology and Oncology.

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Dr. Lan Huang, CEO and Co-Founder
Introduction

Two Near-Term NDAs & Robust Drug Development Pipeline

	Indication / Target	Program	Trial Name / Collaborator	Preclinical	Phase 1	Phase 2	Phase 3	Commercial Rights[1]	Status/Next Milestone
Late stage	CIN (All cancer, all chemo)	Plinabulin + pegfilgrastim	PROTECTIVE-1 & PROTECTIVE-2	Phase 3 primary endpoint met in pivotal data announced November 2020				Global	China and U.S. NDA submission in **March 2021;** currently under regulatory review
	NSCLC (2nd/3rd line)	Plinabulin + docetaxel	DUBLIN-3	Phase 3 second interim analysis completed				Global	Global Final topline Phase 3 data Mid **2021**
Triple Combo IO (IIT)	SCLC	Plinabulin + nivolumab + ipilimumab	10 US sites, including Rutgers University as lead site					Global	Phase 1 completed
	Multi-cancer (2nd/3rd line)	Plinabulin + PD-1/PD-L1 + radiation/chemo	THE UNIVERSITY OF TEXAS MD Anderson Cancer Center					Global	Initiate Phase 1 in 7 cancers **Q2 2021**
Investigator-initiated IO	Oral T cell co-stimulator	BPI-002						Global	
	IKK inhibitor	BPI-003						Global	
	Oral neo-antigen generator	BPI-004						Global	
SEED Therapeutics	KRAS and additional targets	Targeted Protein degradation (TPD, molecule glue platform)	SEED THERAPEUTICS					Global	Potential additional partnerships
	Multiple		Lilly						$800M collaboration

[1]Global rights to Plinabulin ex-China. 58% ownership of Chinese subsidiary, Dalian Wanchunbulin Pharmaceuticals Ltd., which owns Chinese rights to Plinabulin. BeyondSpring owns 100% of global rights to Plinabulin. SEED Therapeutics is a ~60%-owned BeyondSpring subsidiary.

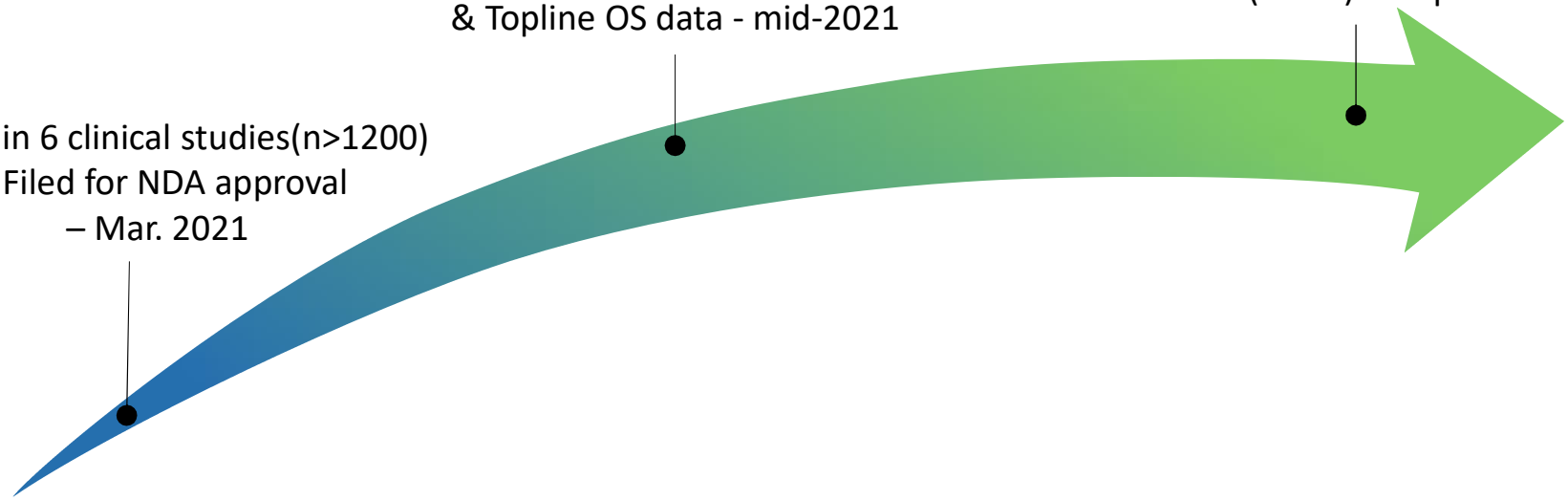
Plinabulin Value Generation Roadmap

Proven → **Expand** → **Transform**

Proven in 6 clinical studies(n>1200) & Filed for NDA approval – Mar. 2021

Phase 3 study fully enrolled (n=559) & Topline OS data - mid-2021

Promising early clinical efficacy data – Jun. 2021 (ASCO) & Expected in 2022



CIN (BTD)
Superior Regimen vs. SOC & NDA Filing in the US and China

NSCLC
Strong MOA Rationale & Promising Preliminary Clinical Data

Multiple Cancers (I/O Combo)
Synergistic MOA with Checkpoint Inhibitors & Promising Preclinical & Early Clinical Efficacy Data

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Plinabulin: “Pipeline in a Drug”

First-in-Class, Selective Immunomodulating Microtubule-Binding Agent (SIMBA)

Building the Plinabulin Franchise

CIN	Anti-Cancer IO Proof of Concept	Anti-Cancer 1st Line Extension
Raise the Standard of Care	DUBLIN-3 in NSCLC Big Ten in SCLC MD Anderson Basket	Expand to 1st Line in 'all' cancers and in 'all' triple combinations

CIN is a Problem with Bone Marrow, Independent of Chemotherapy and Cancer

The Premise

- Chemotherapy kills fast dividing cells, which includes cancer cells, and white blood cells in bone marrow
- CIN is a problem with bone marrow, and not a problem with a specific type of cancer
- All G-CSF and biosimilar G-CSF (including pegfilgrastim) have the same MOA and are interchangeable in use

Broad Label Potential for Plinabulin – G-CSF Combination

- G-CSF class provides a base protection from severe neutropenia in Week 2 following chemotherapy use
- Plinabulin has MoA of protecting neutrophil in Week 1 after chemotherapy, which has been consistently shown in pivotal study (Protective-2 or 106 Phase 3) and 5 supportive studies, that includes various chemotherapies, and in various non-myeloid cancer trials
- **The combination provides increased protection following chemotherapy**

Proposed Label

- Plinabulin when combined with G-CSF is indicated for concurrent administration with a myelosuppressive chemotherapeutic regimen in patients with non-myeloid solid tumor malignancies for the prevention of chemotherapeutic induced neutropenia (CIN)

Favorable Benefit/Risk Ratio (Plinabulin + G-CSF vs. G-CSF alone)

Improved Efficacy (ANC based in Cycle 1) – 106 Phase 3	Improved Efficacy (FN) – 106 Phase 3	Favorable Safety – 106 Phase 2+3
No Grade 4 Neutropenia • 31.5% vs. 13.6% (incidence), p=0.0015 **No Grade 3/4 Neutropenia** • 4.55% vs. 20.72% (incidence), p=0.0003 **Mean ANC Nadir** • 0.54 vs. 0.31 (x 10^9 cells/L), p=0.0002 **DSN Cycle 1 day 1-8** • 1.1 day vs. 1.4 day, p=0.0065 **DSN Cycle 1** • 1.2 day vs. 1.5 day, p=0.0324 **Profound Neutropenia** • 21.6% vs. 46.4% (incidence), p=0.0001 • 0.3 day vs. 0.6 day (duration), p=0.0004	**FN** • 3.6% vs. 6.3% (incidence) • 0.9% vs. 3.6% (grade 4 incidence) • 1.25 day vs. 2.28 day (duration) **Hospitalization for FN patients** • 75% vs. 100% • 3.75 day vs. 7.14 day (duration) **Change of Chemo dose/regimen in later cycles** • 2.7% vs 6.3%	**Grade 4 TEAE** • 20% less Grade 4 TEAEs in the combination (55.9%) compared to pegfilgrastim alone (75.8%) **SAEs** • Higher SAE frequency, however, less Grade 4 and more Grade 3 events **AEs leading to discontinuation** • Similar frequency, mostly single events **Bone pain (AE)** • 6.3% bone pain in the combination vs. 28.0% in pegfilgrastim **Low grade GI track side effects and transient hypertension**

Plinabulin's Regulatory strategy for CIN: Superior Profile in a Broad Label - NDA Accepted by FDA with Priority Review (PDUFA date 11/30/2021)

Plinabulin shown to statistically reduce Grade 4 neutropenia in 6 clinical trials (1,200+ patients)

Supporting Studies

Plinabulin vs. placebo (Study 101, Dublin-3)

- Grade 4 reduction highly statistically significant (Study 101 and DUBLIN-3, $p<0.0003$ and $p<0.0001$ respectively)

Registration Study

Plinabulin + G-CSF combo vs. G-CSF mono (Protective-2, phase 3)

- Superior CIN prevention in primary and key secondary endpoints

MOA support from 5 additional studies:

Plinabulin early onset in Week 1, G-CSF effect in Week 2

Supporting Studies

Plinabulin vs. G-CSF (Protective-1, phase 2 +3)

- Non-inferior CIN activity
- Superior adverse event profile: limited bone pain, limited platelet reduction, and limited immune suppression[1]

700+ cancer patients treated with Plinabulin (various doses)

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1. Blayney et al. JAMA Oncology 6(11): e204429 (2020)

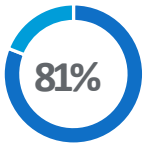
Neutropenia Vulnerability Gap

Plinabulin's Commercial Plan is purpose-built to elevate the standard of care and drive commercial performance

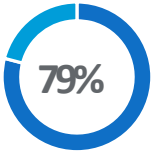
Only plinabulin can cover the NVG – day 1 to day 10 – with the potential to elevate the standard of care in CIN

The plinabulin combo: the perfect pairing to improve protection for patients & provide greater control for oncologists

Market Concentration/Growth



360 multi-center accounts use the vast majority of CIN prophylaxis

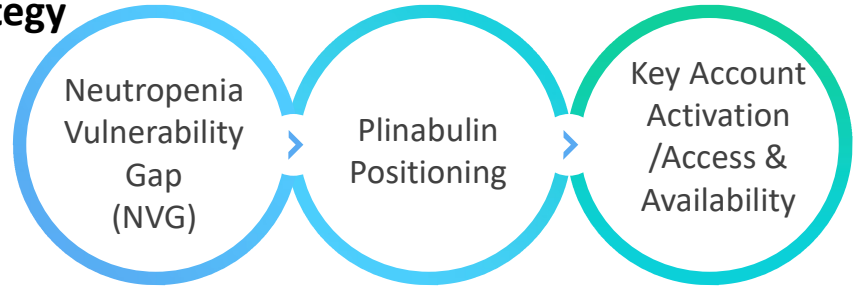


Four cancer types represent nearly 80% of CIN prophylaxis Breast, Lung, Pancreatic & CRC

Growing market:

- 100% increase in the addressable market
- 1.4 M G-CSF cycles/year (U.S.)

Go-to-market Strategy



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Dr. Ramon Mohanlal, CMO and EVP R&D

Oncology Development Strategy

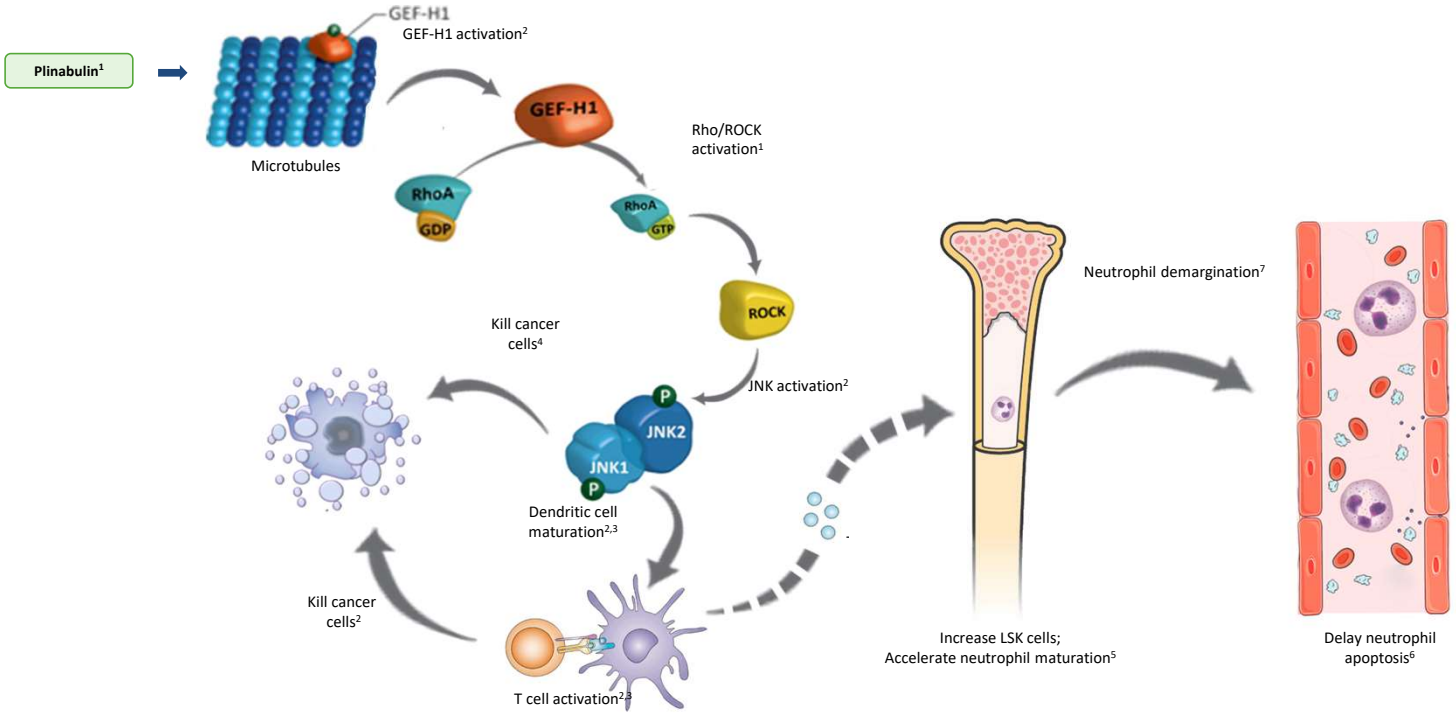
BeyondSpring Triple IO Combination Strategy with Plinabulin

Plinabulin Summary

- **Small Molecule**
  - Simple manufacturing process (3-step Synthesis)
- **Given by IV Infusion**
  - Infusion on the same day of the Chemotherapy
- **MoA:**
  - *Primarily* through **Immune-Enhancement for Anti-cancer activity**
    - Plinabulin is a Dendritic Cell Activation/Maturation enhancer
  - Plinabulin also has **direct anti-cancer activity** in a number of cancers:
    - SCLC
    - CNS cancers
    - Sarcoma
    - TNBC
    - Gastric Cancer
    - Bladder Cancer

Safety Data with plinabulin in >700 patients demonstrating a favorable safety and tolerability profile

Plinabulin: First-in-Class Agent, Stimulating Innate and Adaptive Immune System (Proven Target: Immune Defense Protein GEF-H1)



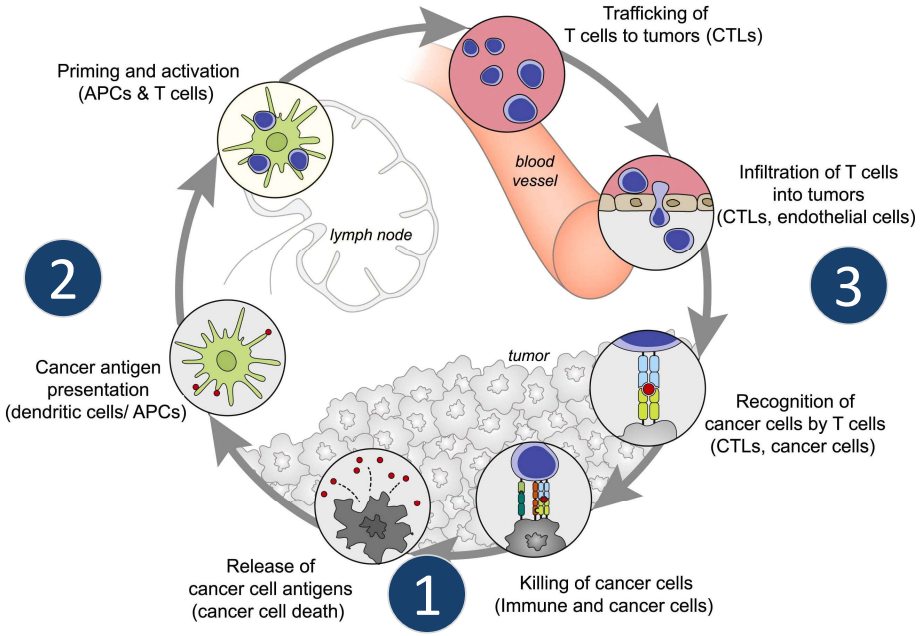
Note: [1] La Sala et al., 2019 Chem. [2] Kashyap et al., 2019 Cell Reports. [3] Zhang et al., 2005 Mol Cell Biol. [4] Singh et al., 2011 Blood. [5] Suwa et al., 2000 Am J Physiol Heart Circ Physiol; Ghosh et al., 2018 ACR Annual Conference; Blayney et al., Society of Leukocyte Biology. [6] Asensi et al., 2004 Infection and Immunity.

Plinabulin Induces Dendritic Cell Maturation, a Key Step in Initiating Anti-cancer Durable Response in IO Combo

2 Plinabulin

Stimulate maturation of dendritic cells to increase antigen presentation

Dendritic cells are the most important antigen-presenting cells



3 Checkpoint Inhibitors

Optimize T cell response

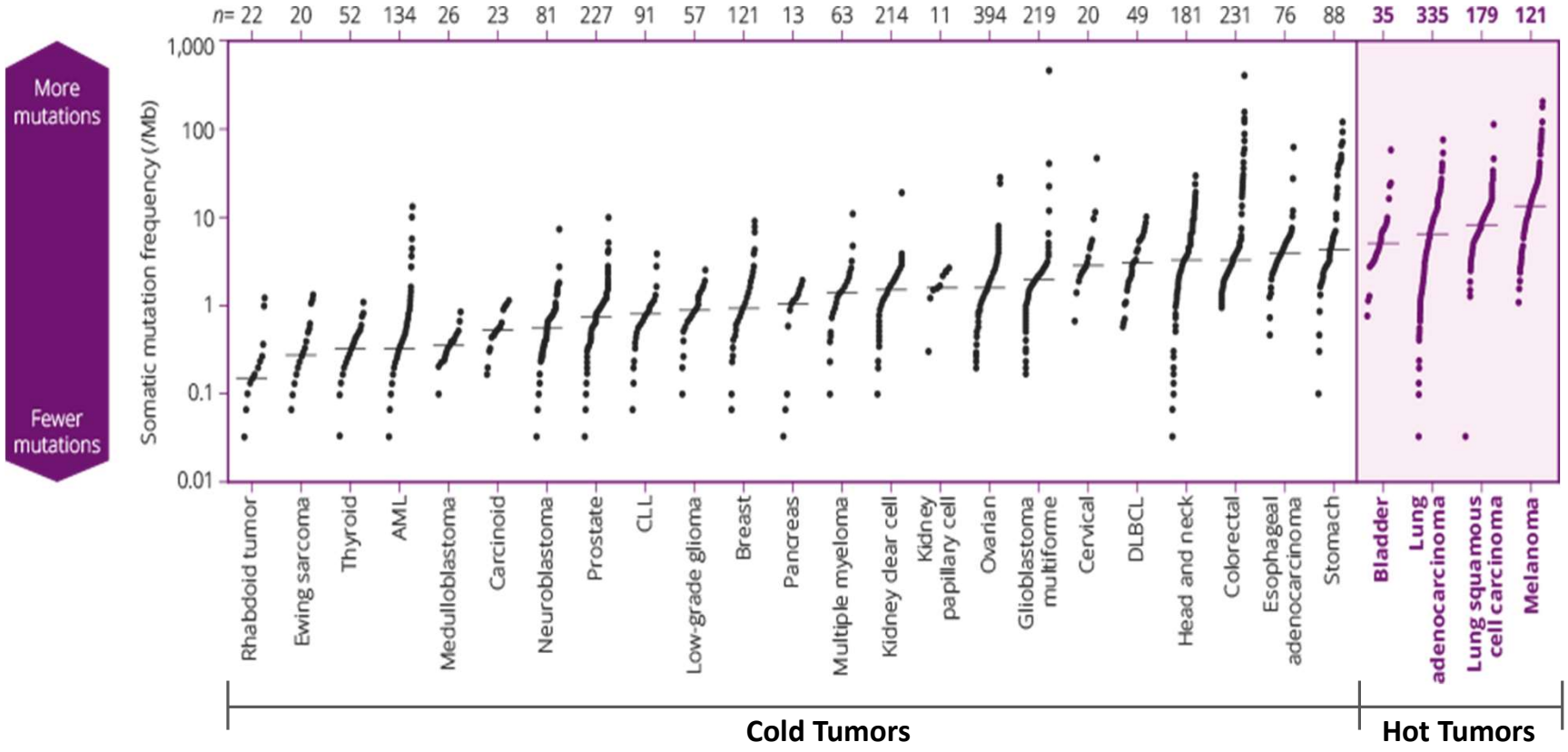
1 Radiation/Chemotherapy/ Plinabulin

Release Tumor Antigens

For more potent anti-cancer effect

1 + 2 + 3 → Optimal Immuno-Oncology Response

‘Hot’ and ‘Cold’ Tumors



BeyondSpring’s Approach to ‘Cold 'Tumors

- **Neo-Antigen Generator + Plinabulin + PD1/PD-L1 Inhibitor**

‘Hot’ versus ‘Cold’

‘Hot’ Tumors are Immune Responsive

- Harbor intrinsically tumor antigens/immunogens capable of stimulating the Immune System
- Need something that generates/releases these antigens/immunogens
  - That ‘something’ can be Radiotherapy of Chemotherapy (or Plinabulin)
- Today, Checkpoint Inhibitors are effective in ‘Hot’ Tumors

‘Cold’ Tumors are not Immune Responsive

- Majority of human cancers
- PD1/PD-L1 inhibitors are not candidate treatments
  - For PD1/PD-L1 agents to be effective, ‘Cold’ tumors need to be converted to ‘Hot’
- Converting ‘Cold’ to ‘Hot’ is a tremendous next wave opportunity
  - Area of focus for BeyondSpring

BeyondSpring Approach to 'Hot' Tumors

1. **Combination Plinabulin +Radiotherapy+ PD1/PD-L1**
   - Triple Combination in collaboration with MD Anderson, currently in Phase 1

2. **Combination Plinabulin +Chemotherapy+ PD1/PD-L1**
   - In preparation

3. **Combination Plinabulin +PD1/PD-L1 Inhibitor+CTLA-4 Inhibitor**
   - For 'Hot' tumors where Plinabulin has direct anticancer effect
     - Plinabulin act as the antigen-generator and Dendritic Cell maturator
       - **SCLC :** With Nivolumab/Ipilimumab currently in Phase 2
       - CNS cancers
       - Sarcoma
       - TNBC
       - Gastric Cancer
       - Bladder Cancer
       - Other

Plinabulin as a 'Universal' Add-On in Cancer Therapy

Plinabulin has the potential to add to Survival Benefit, but also prevents CIN and IR-AEs

- **In combination with PD1/PD-L1 inhibitor + Chemotherapy :**
  - Survival benefit
  - Less CIN
  - Less IR-AEs

- **In combination with Nivolumab + Ipilimumab**
  - Survival benefit
  - Less IR-AEs

Immune-Related AEs (IR-AEs)

- CIN is the most prevalent and rate-limiting toxicity for Chemotherapy

- The CIN equivalent for IO therapy is IR-AEs
  - In particular with IO/IO combinations such as
    - Nivolumab/Ipilimumab
    - Durvalumab/Tremelimumab

  - Grade 3/4 IR-AEs generally lead to permanent discontinuation of the IO therapy
    - Typically treated with steroids
    - Grade 3/4 IR/AEs with Nivolumab/Ipilimumab in SCLC is ~40% of patients

Plinabulin may prevent IR-AEs due to Inhibition of PDE4

Development Strategy

- **Randomized two-arm Head-to-Head comparison trials require large sample size per arm in Phase 1/2 (>n=100) to demonstrate PoC**
  - Not cost-effective

- **The approach we take is reversal of resistance PD1/PD-L1 therapy**

  - We maintain the same PD1/PD-L1 on which the patient's disease progressed, and add Plinabulin +/- other agent with the aim to convert the observed resistance into response

  - The patient serves as their own control
    - Small number of patients (~n=10 or less) to demonstrate PoC

    - Once we have preliminary confirmation, we plan to move forward with a larger trial

Current Studies with Plinabulin for the Anti-Cancer Application

1. **DUBLIN-3: Phase 3**
   - Plinabulin + Docetaxel vs Docetaxel alone in NSCLC

2. **Big Ten Triple Combination: Phase 2**
   - Plinabulin + Nivolumab + Ipilimumab in SCLC

3. **MD Anderson Triple Combination: Phase 1**
   - Plinabulin + PD1/PD-L1 Inhibitor + Radiotherapy in a basket of solid tumors

4. **Additional Studies in Preparation**

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Dr. Ramon Mohanlal, CMO and EVP R&D

Big Ten SCLC Study

A phase I trial of plinabulin in combination with nivolumab and ipilimumab in patients with relapsed small cell lung cancer (SCLC): Big Ten Cancer Research Consortium (BTCRC-LUN17-127) study

Jyoti Malhotra[1], Nasser H. Hanna[2], Alberto Chiappori[3], Lawrence E. Feldman[4], Naomi Fujioka[5], Igor I. Rybkin[6], Shadia I. Jalal[2], Malini Patel[1], Dirk Moore[1], Chunxia Chen[1], Salma K. Jabbour[1]

[1]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; [2]Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; [3]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [4]University of Illinois Hospital & Health Sciences System, Chicago, IL; [5]Univ of Minnesota, Minneapolis, MN; [6]Henry Ford Cancer Institute, Detroit, MI

BACKGROUND

- Plinabulin (BPI-2358) is a first-in-class, Selective immunomodulating Microtubule-Binding Agent (SIMBA) by inducing dendritic cell maturation, leading to T cell action.
- Preclinical studies report that plinabulin potentiates the cytotoxicity of dual checkpoint inhibition (CPI) with nivolumab and ipilimumab.
- Plinabulin may also reduce immune-related AEs from CPI through its phosphodiesterase-4 (PDE4) inhibitory activity which is associated with anti-inflammatory effects.
- We report initial results from a Phase I study assessing plinabulin in combination with nivolumab and ipilimumab (**NCT03575793)**.

METHODS

- In this dose-escalation phase I study, patients with extensive-stage SCLC who had progressed on or after prior platinum-based chemotherapy (±PD-1/PD-L1) were enrolled using a 3+3 design.
- **Primary objective** was to determine dose-limiting toxicities (DLT's) and recommended Phase 2 dose (RP2D).
- Patients received treatment as till progression or intolerable toxicity.
- Patients were evaluable for DLT if they received at least 2 cycles of therapy; **DLT period** was defined as the first 6 weeks from C1D1.
- Secondary endpoints were ORR, PFS and frequency of irAEs. Correlative analysis included inflammatory biomarkers: hsCRP, ESR, SAA and haptoglobin.

Treatment Schema

Day 1, Cycles 1-4
(cycle = 21 days)
Nivolumab: 1 mg/kg
Ipilimumab: 3 mg/kg
Plinabulin:
- (-1) 13.5 mg/m^2
- (start) 20 mg/m^2
- (+1) 30 mg/m^2

↓

Day 1, Cycles 5+
(cycle = 14 days)
Nivolumab: 240 mg
Plinabulin: as above

RESULTS

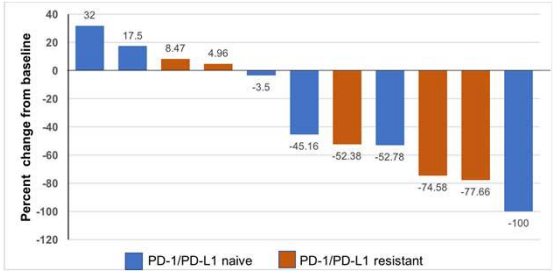
- Between 9/2018 and 11/2020, 17 patients were enrolled (1 patient withdrew consent before treatment, 16 were evaluable for safety)
- Median age was 59 years (range 43 to 78); 9 (56%) patients were female; 10 (63%) had received prior CPI.

Treatment-related adverse events

	All grade	≥ Grade 3
Nausea	10 (63%)	0
Infusion reaction	8 (50%)	1 (6%)
Vomiting	7 (44%)	0
diarrhea	7 (44%)	1 (6%)
Fatigue	6 (32%)	1 (6%)
Pyrexia	4 (25%)	0
Rash	3 (19%)	0
Hypertension	3 (19%)	1 (6%)

- Eight patients were treated at dose-level 1 of plinabulin (20 mg/m^2) and 8 patients at 30 mg/m2 of plinabulin (level 2); **dose-level 2 was determined to be RP2D.**
- There were **2 DLTs**; 1 at dose-level 1 (grade 3 altered mental status lasting < 24 hours) and 1 at dose-level 2 (grade 3 infusion reaction).
- Eight patients (50%) had at least one grade 3 or higher treatment-related AE; there were no treatment-related deaths.
- **Immune-related AEs:** Three patients (19%) had grade 3 or higher irAEs; only 1 at MTD/dose-level 2 (12.5%). The AEs were colitis, transaminitis and elevated lipase, all resolved with steroids without sequelae.

Waterfall plot of best overall response in target lesions compared to baseline

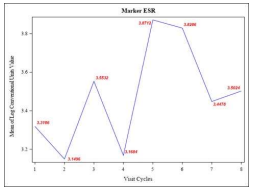


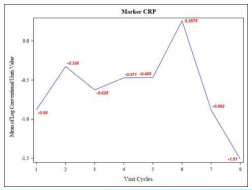
RESULTS

- Thirteen patients were evaluable for efficacy (1 withdrew consent, 1 death from unrelated cause, 1 replaced for DLT); 6 patients had PR (ORR 46%)
- There were 3 PRs in **PD-1/PD-L1 therapy naïve patients (3/6; 50%)**
- There were 3 PRs in **PD-1/PD-L1 resistant patients (3/7; 43%). These 3 patients continued on treatment for 3 months, 5 months (still on treatment) and 18 months.**

Inflammatory biomarker correlative analysis

Levels of high sensitivity C-reactive protein [hsCRP], erythrocyte sedimentation rate [ESR] and serum amyloid A [SAA] were measured in whole blood on day 1 of each cycle. Figure below shows the plots of log-transformed values for the mean at each cycle. Levels of hsCRP, ESR and SAA transiently increased around cycle 4 before returning to baseline values.





CONCLUSIONS

- Plinabulin in combination with nivolumab and ipilimumab was safe and well tolerated with promising efficacy signal of 46% ORR.
- The combination is shown to re-sensitize the previous failed PD-1/PD-L1 patients with ORR at 43%, and treatment lasting to as long as 18 months.
- A phase 2 study in CPI-experienced patients with relapsed SCLC is planned to confirm the preliminary signals of clinical activity and reduced immune toxicity.

Funding: BeyondSpring Pharmaceuticals, Bristol Myers Squibb

Triple I/O Combo Development for Multiple Cancer Indications in PD-1/PD-L1 Failed Patients – Severe Unmet Medical Needs

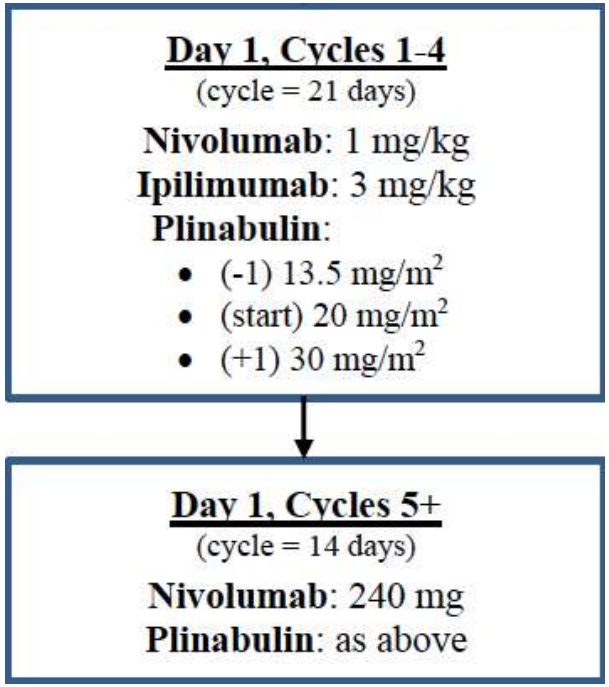
	Indication / Target	Program	Trial Name / Collaborator	Commercial Rights	Status
Triple Combo IO (IIT)	SCLC Checkpoint naïve and checkpoint refractory patients	Plinabulin + Nivolumab (PD-1) + Ipilimumab (CTLA-4)	6 US sites, including Rutgers University as lead center (Big Ten)	Global	Phase 1 completed, Presented at ASCO June 2021
	SCLC Checkpoint refractory patients	Plinabulin + Nivolumab (PD-1) + Ipilimumab (CTLA-4)	Big Ten Study	Global	Initiated Phase 2
	7 Cancers* PD-1/PDL1 failed pts	Plinabulin + PD-1/PD-L1 + radiation/chemo	MD Anderson	Global	Initiated Phase 1 in 7 cancers in Q2 2021

*NSCLC, SCLC, Renal Cell, Bladder, Merkel Cell, Melanoma, Cancers with high levels of microsatellite instability

Plinabulin + Nivolumab + Ipilimumab in SCLC: Study Design

Dose-escalation Phase I study 3+3 Design

- In patients with extensive-stage SCLC who had progressed on or after prior platinum-based chemotherapy (±PD-1/PD-L1)



Primary objective

- To determine dose-limiting toxicities (DLT's) and recommended Phase 2 dose (RP2D).
  - Patients received treatment until progression or intolerable toxicity.
  - Patients were evaluable for DLT if they received at least 2 cycles of therapy
  - DLT period was defined as the first 6 weeks from C1D1.

Secondary endpoints:

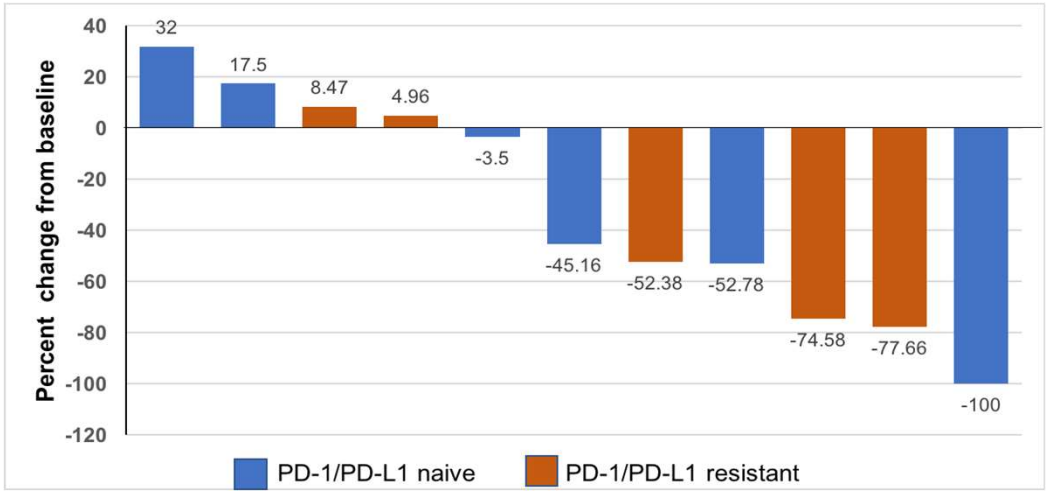
- ORR, PFS
- Frequency of Ir-AEs.

Efficacy Analysis

Data cutoff –December 30,2020

Efficacy Analysis	PD-1/PD-L1 therapy naïve (n= 6)	PD-1/PD-L1 resistant (n=7)
Number of patients with PR	3 (50%)	3 (43%)

*PR –Partial Response - RESIST 1.1 : At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

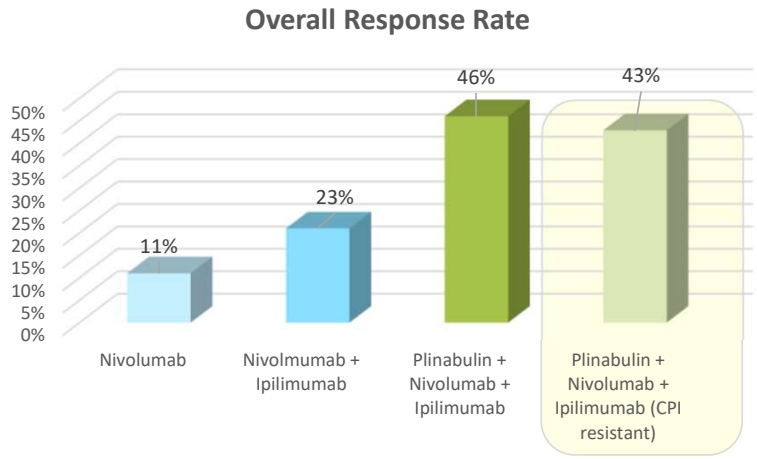


Waterfall plot of best overall response in target lesions compared to baseline

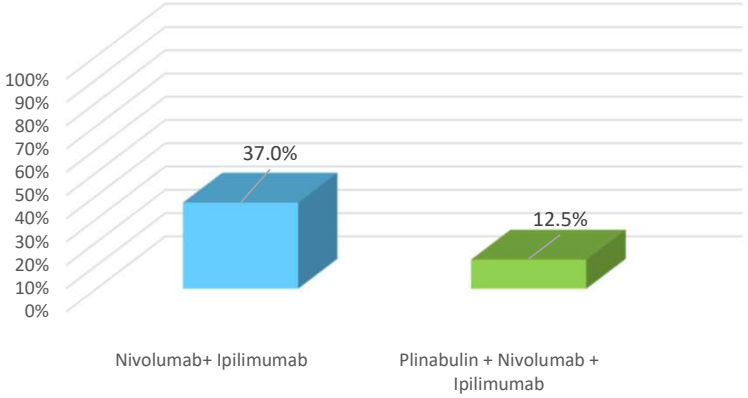
- 13 patients were evaluable for efficacy
  - 1 withdrew consent
  - 1 death from unrelated cause
  - 1 replaced for DLT
- 6 patients had PR (ORR 46%)
  - There were 3 PRs in PD-1/PD-L1 therapy naïve patients (3/6; 50%)
  - There were 3 PRs in PD-1/PD-L1 resistant patients (3/7; 43%)
  - These 3 patients continued treatment for 3 months, 5 months (still on treatment) and 18 months

Plinabulin + Nivolumab + Ipilimumab in SCLC: Big Ten ITT Phase 1 Study

Efficacy Summary



Immune-Related AE Summary



1.Iams, W.T., Porter, J., Horn, L. Immunotherapeutic approaches for small cell lung cancer, Nat Rev Clin Oncol, 2020 May;17(5):300-312.

Plinabulin in Combination with Nivolumab/Ipilimumab in SCLC

Data	Conclusion
High response rate to previous CPI failures (43%)	Immune system re-sensitized
Improved Anti-cancer Response (46% ORR vs. 12-23% CPI)	Increased antigen presentation simulates T cell activation
Durable response (1 pt on combo for 18 M vs. PFS 1.4-2.6 M for CPI)	Immune response contributes to long treatment duration

This trial with plinabulin in combination with Nivolumab/Ipilimumab in SCLC serves as PoC

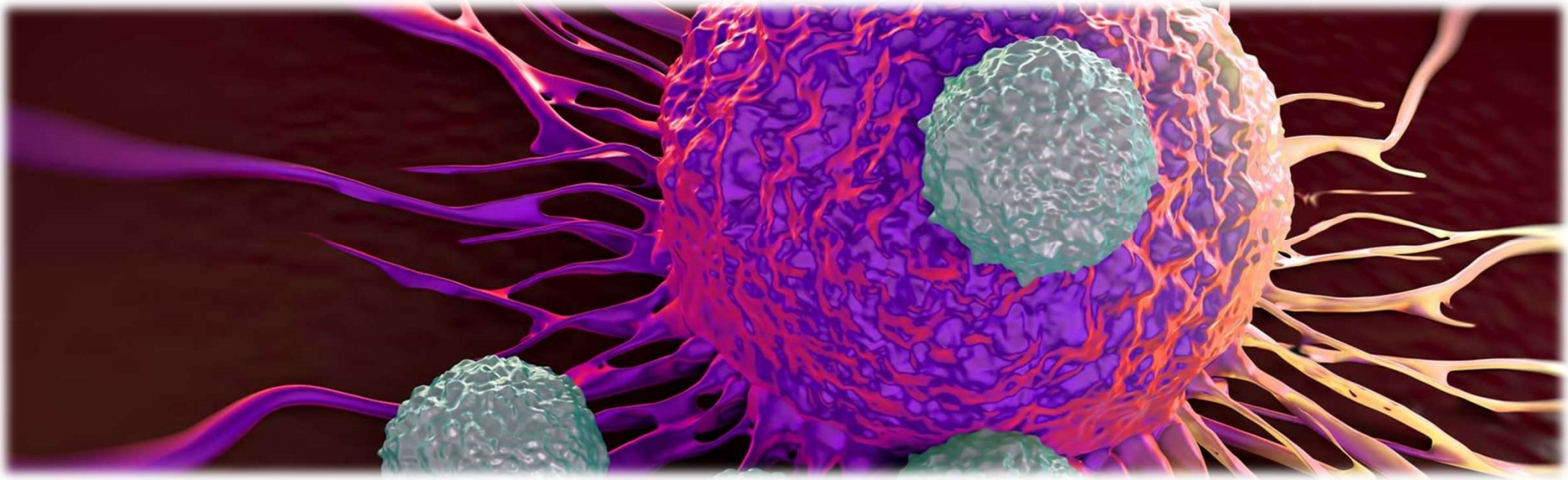
If it works here, we expect it will work in multiple cancer types in which plinabulin exerts anti-cancer effects

- (CNS cancers, Sarcoma, TNBC, Gastric Cancer, Bladder Cancer, Other)

BeyondSpring

Dr. Steven Lin

MD Anderson Triple Combination



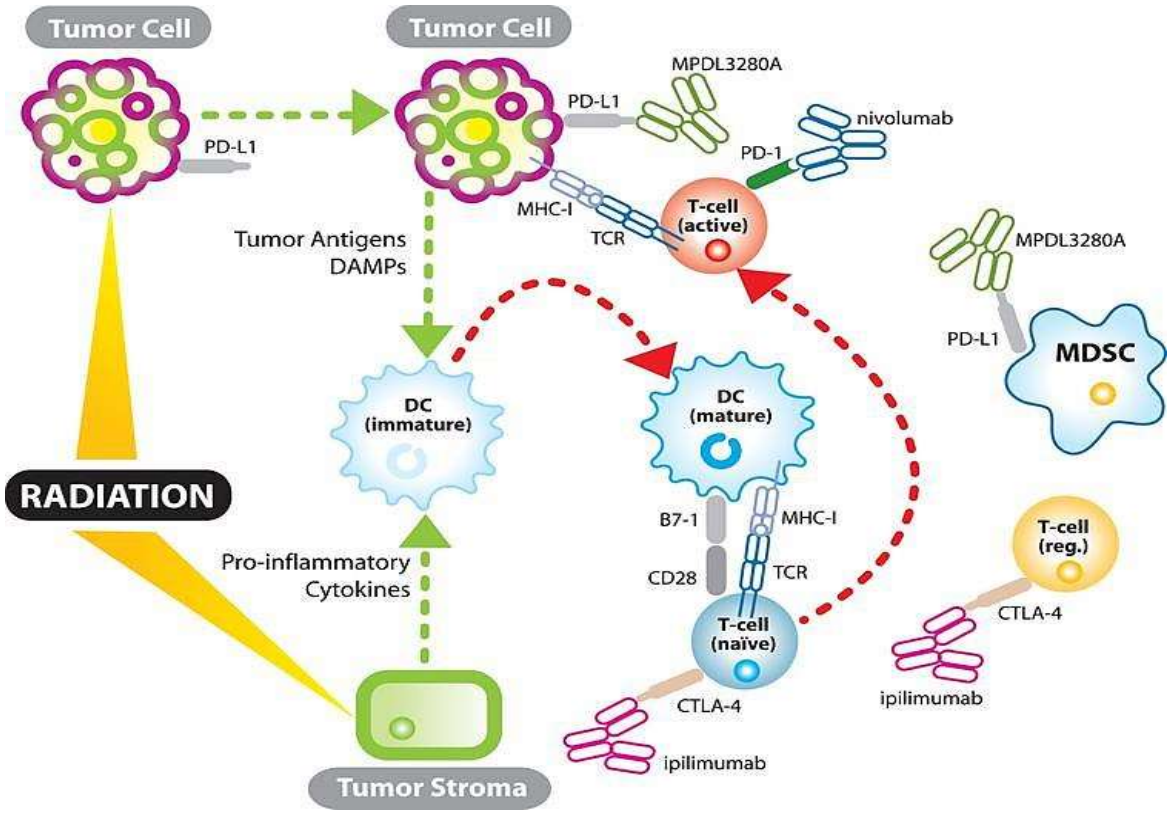
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

BeyondSpring PHARMACEUTICALS

2020-0296: An Open-label, Single-center, Phase 1b/2 Study to Evaluate the Safety of Plinabulin in Combination with Radiation/Immunotherapy in Patients with Select Advanced Malignancies after progression on PD-1 or PD-L1 Targeted Antibodies

PI: Vivek Subbiah, MD, Investigational Therapeutics
Co-PI: Steven H. Lin, MD, PhD, Radiation Oncology

Interplay of cytotoxic agents with DC maturation

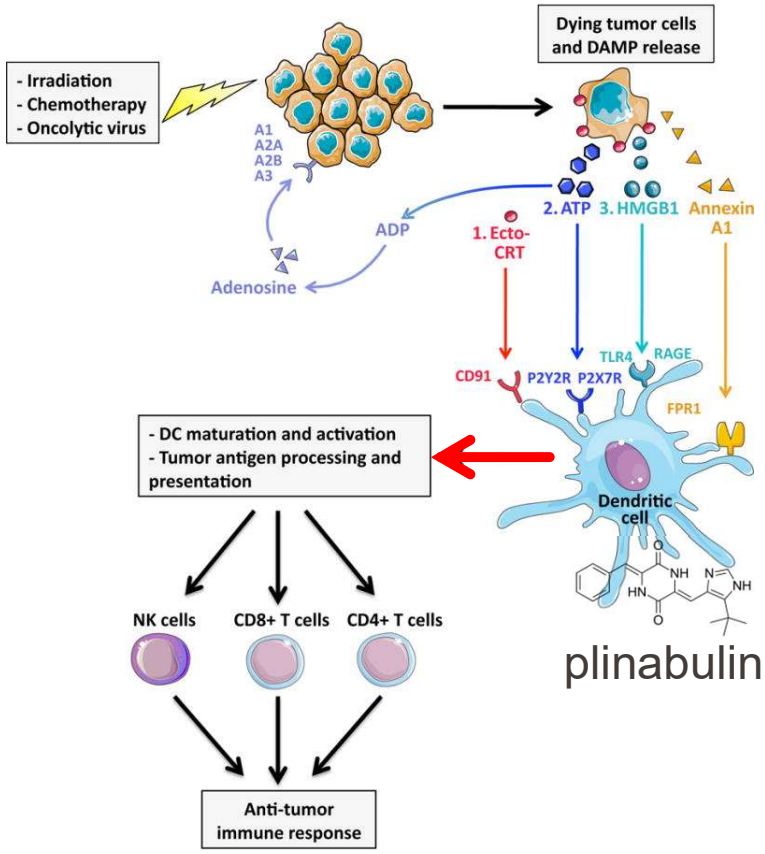


Zackary B and Efstathiou J, Bladder Cancer 2015

Does plinabulin with RT enhance the anti-tumor immune response?

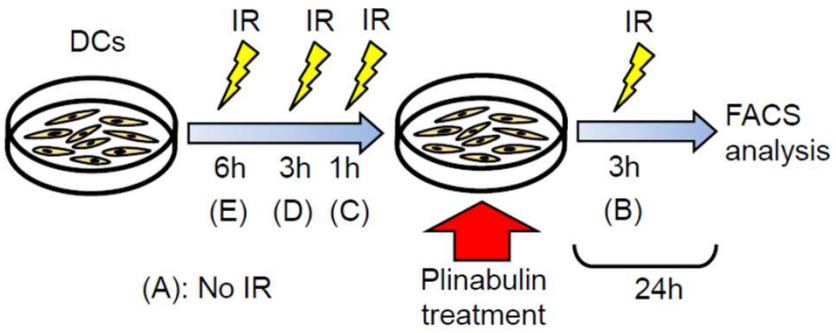
- **What is the proper sequencing of plinabulin and RT?**
  - For radiation sensitization, the sequencing of Drug → RT is important since loading the tumor cells ahead of RT would help sensitize the cells to the effect of RT
- Does pre-activating the dendritic cells with plinabulin enhance the RT response,

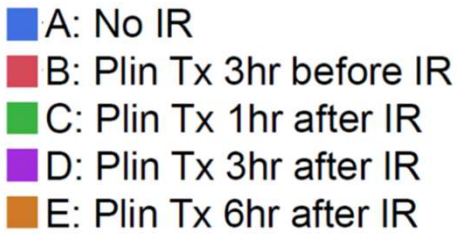
  or
- Does "RT priming" needed to enhance the response?

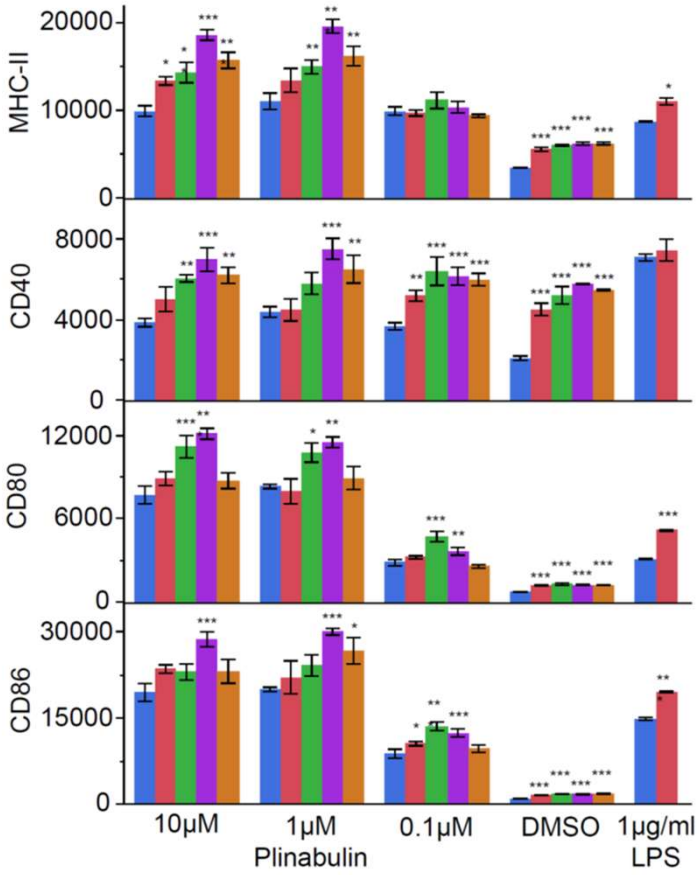


Hernandez C et al., Oncogene 2016

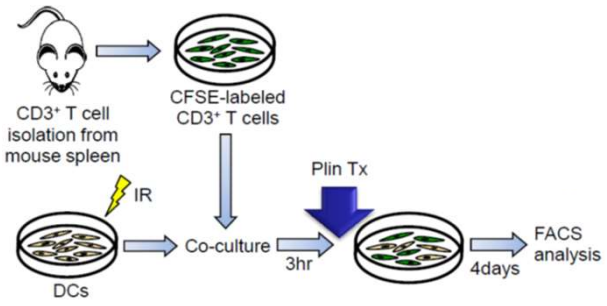
Optimal Sequencing of IR with Plinabulin to elicit DC activation

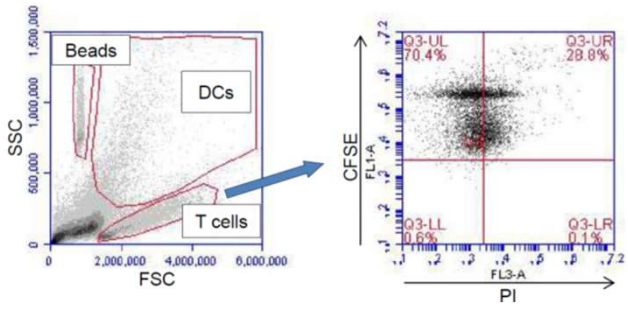


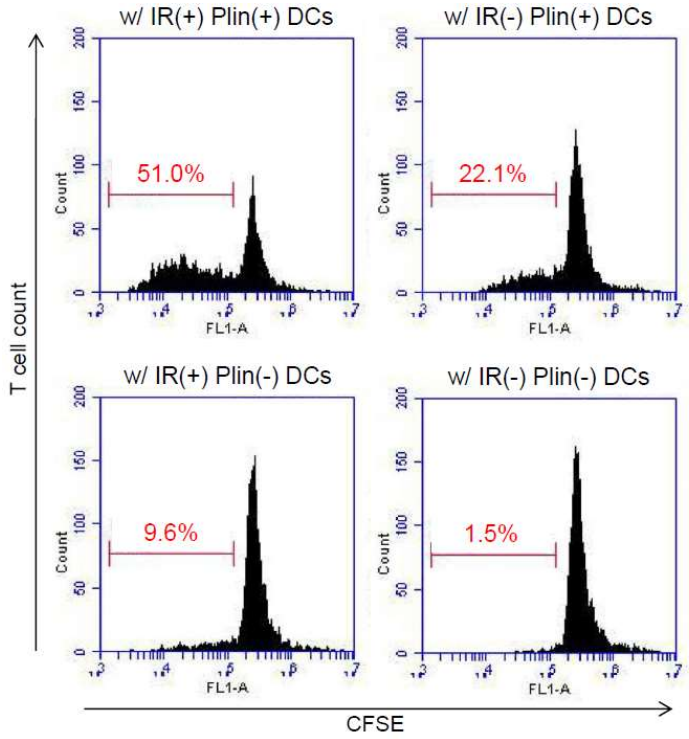


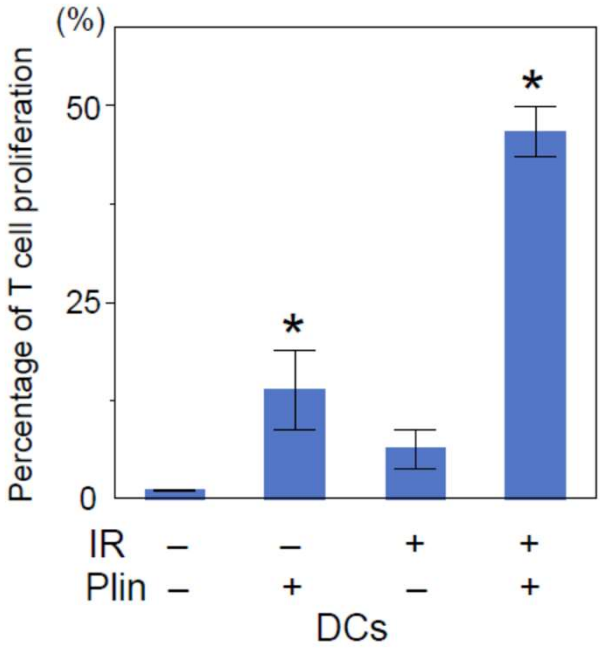


Plinabulin + RT enhances T-cell proliferation in mixed lymphocyte reaction

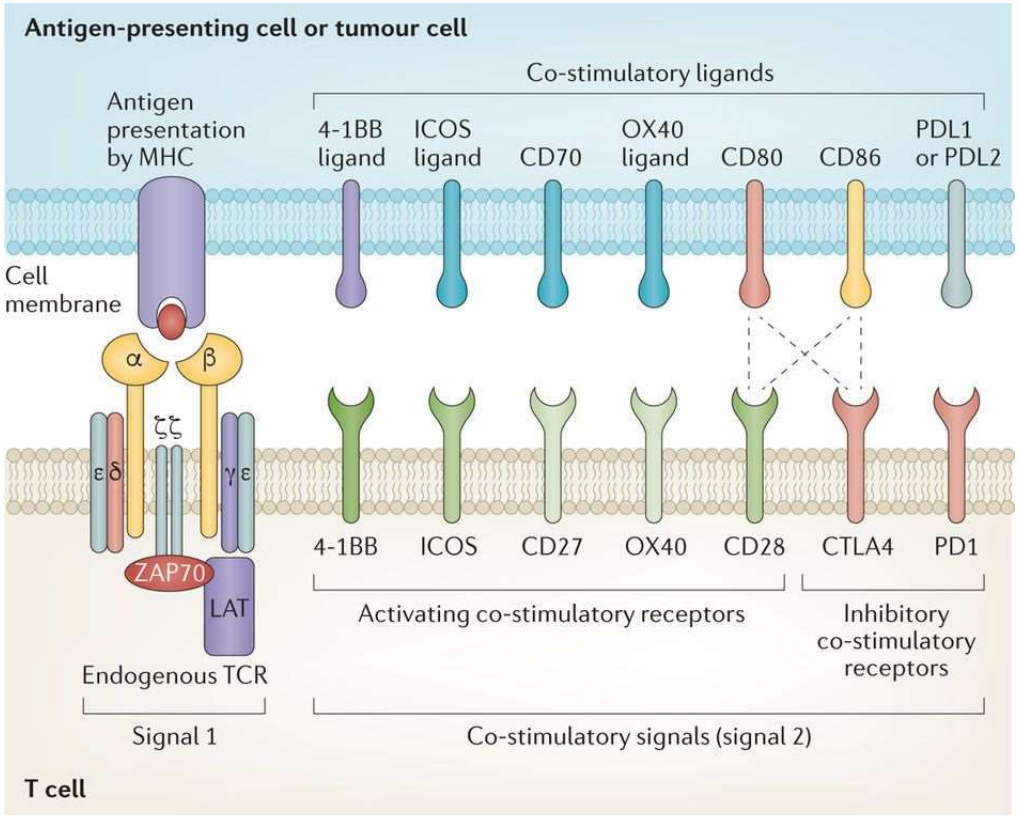








T-cell co-stimulatory molecules besides CD80/86



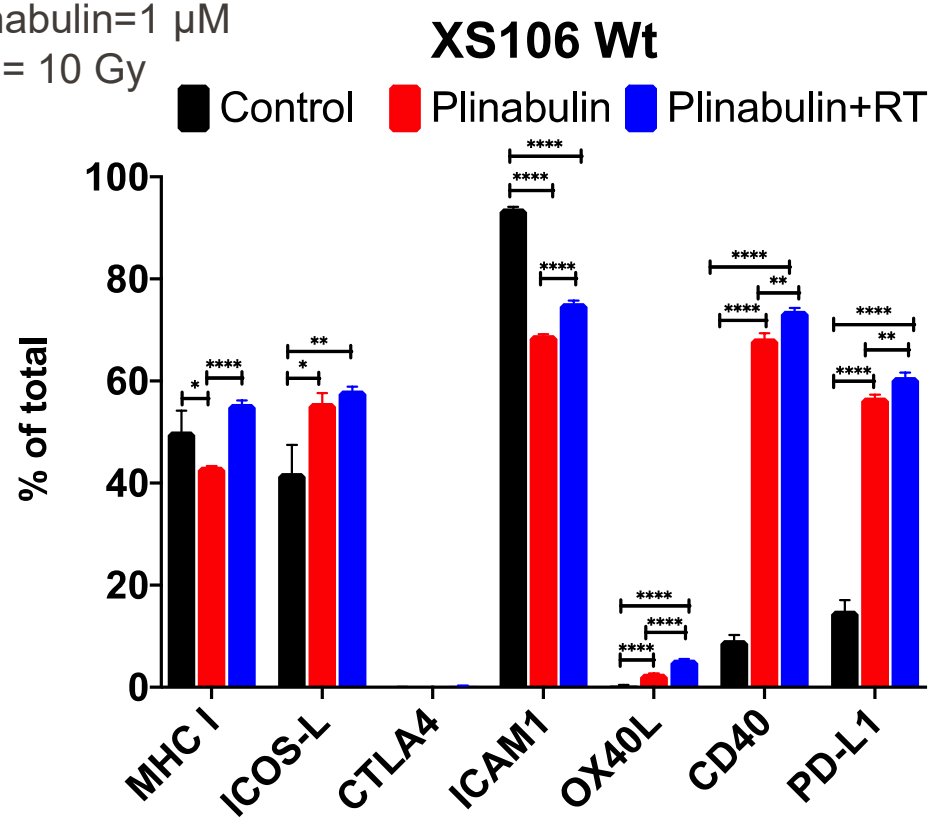
1. MHC-1 complex -provides the primary signal for T cell activation
2. ICAM-1- Cell adhesion molecule helps increase the contact between APC and T cells thus increasing APC mediated T cell proliferation
3. CD40: Immune costimulatory molecule
4. ICOS-L
5. OX40L

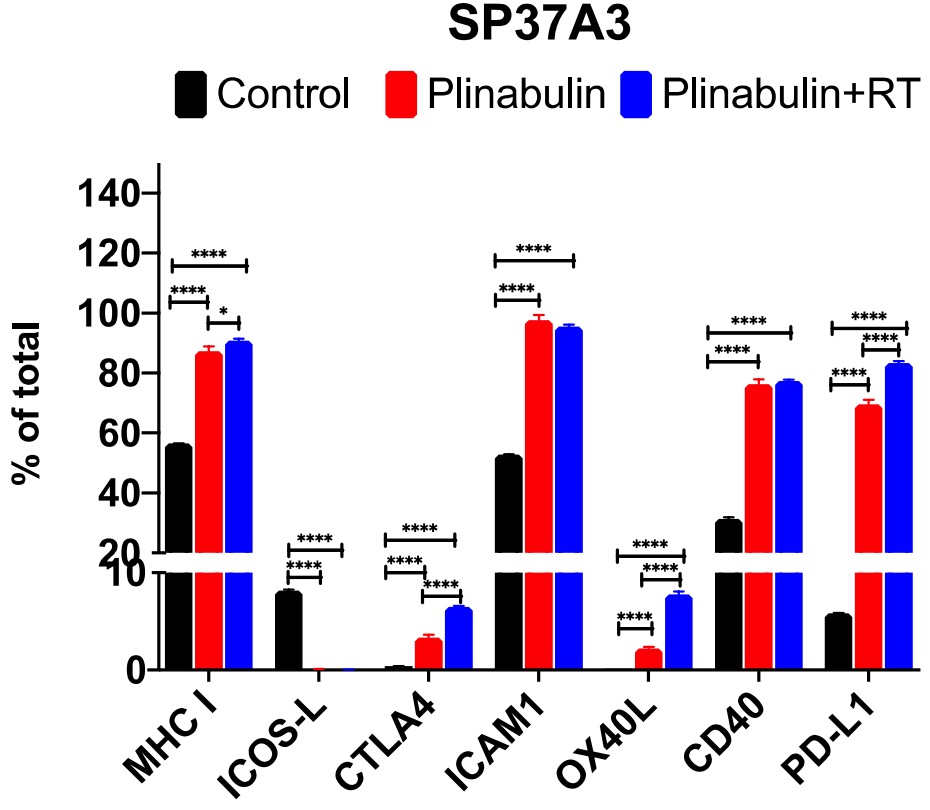
   Additional signal for activating T cells
6. CTLA-4
7. PDL-1

   Negative regulators of T cells

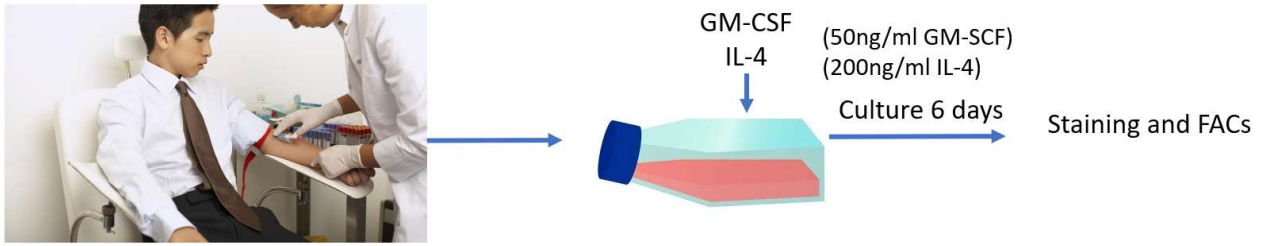
Preliminary results: Plinabulin increase PD-L1 along with co-stimulatory molecules, some augmented by RT

Plinabulin=1 μM
RT = 10 Gy

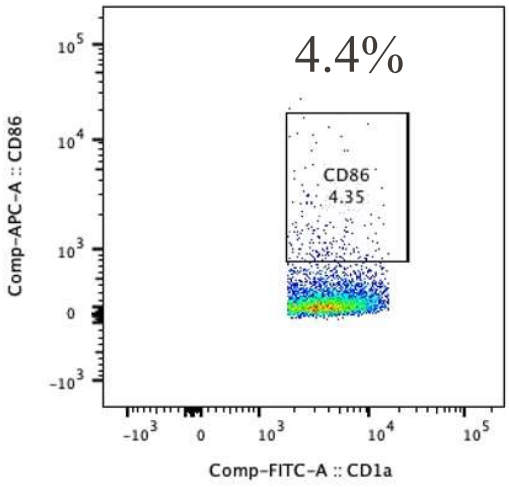




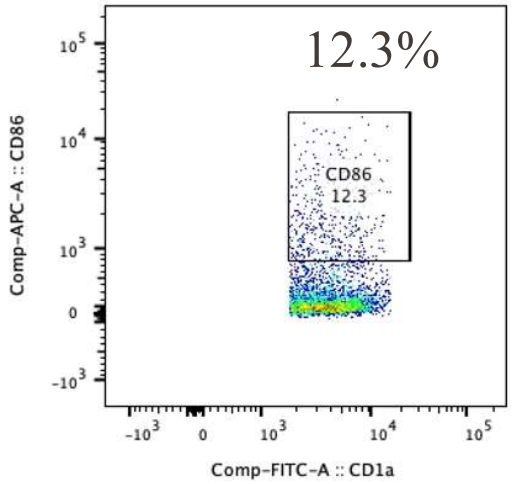
Human PBMC derived DCs: Plin stimulated CD86



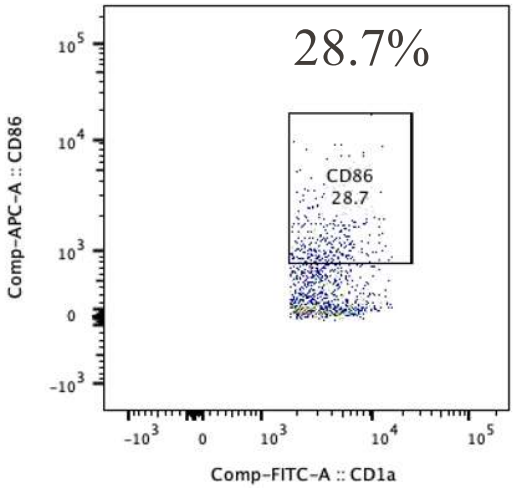
Control



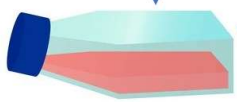
Plinabulin 1 μM



Plinabulin 10 μM



Human PBMC derived DCs: Plin upregulate PD-L1



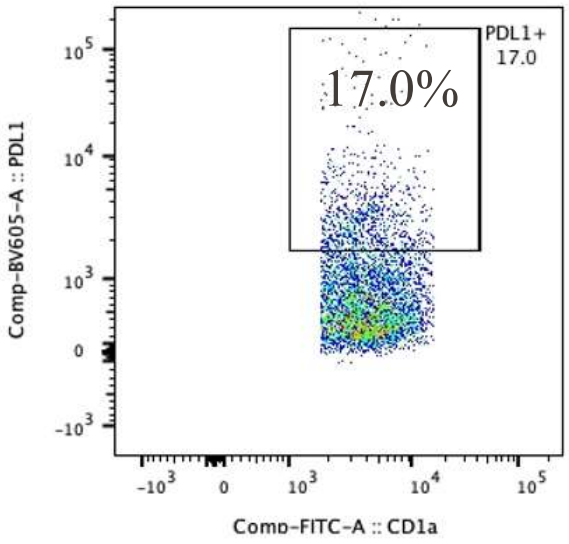
GM-CSF
IL-4

(50ng/ml GM-SCF)
(200ng/ml IL-4)

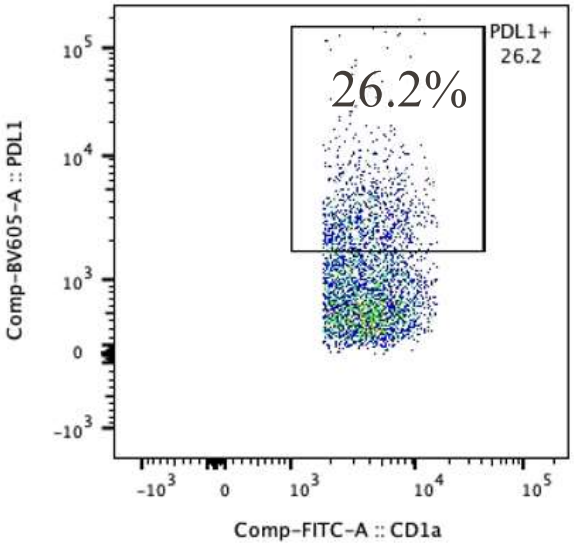
Culture 6 days

Staining and FACs

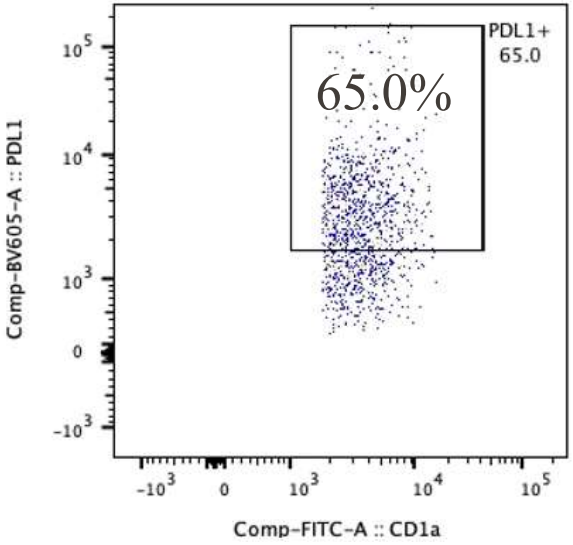
Control



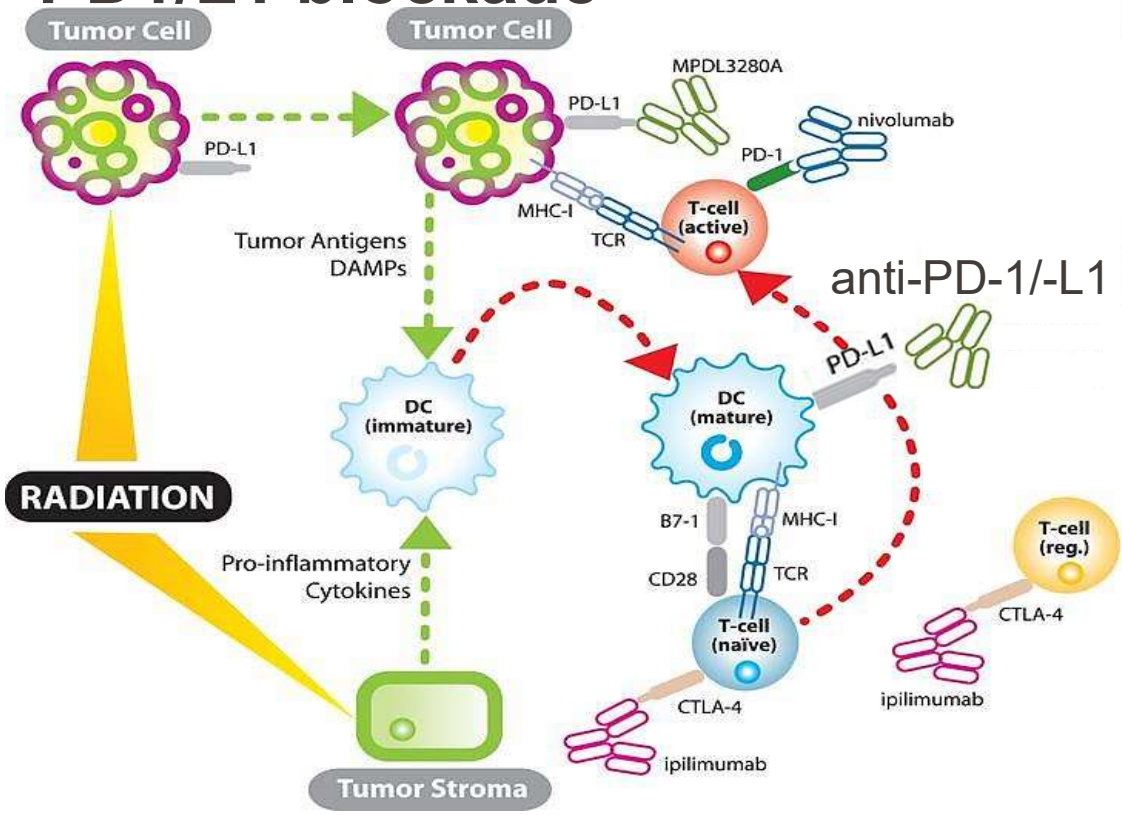
Plinabulin 1 μM



Plinabulin 10 μM



Induced PD-L1 upon DC activation necessitates anti-PD1/L1 blockade



Zackary B and Efstathiou J, Bladder Cancer 2015

nature cancer
ARTICLES
https://doi.org/10.1038/s43018-020-0075-x
Check for updates

PD-L1 expression by dendritic cells is a key regulator of T-cell immunity in cancer

Soyoung A. Oh[1], Dai-Chen Wu[1,5], Jeanne Cheung[1], Armando Navarro[1], Huizhong Xiong[1], Rafael Cubas[1], Klara Totpal[1], Henry Chiu[1], Yan Wu[1], Laetitia Comps-Agrar[1], Andrew M. Leader[2,3,4], Miriam Merad[2,3,4], Merone Roose-Germa[1], Soren Warming[1], Minhong Yan[1], Jeong M. Kim[1,6], Sascha Rutz[1] and Ira Mellman[1]✉

NATURE CANCER | VOL 1 | JULY 2020 | 681–691 | www.nature.com/natcancer

nature COMMUNICATIONS

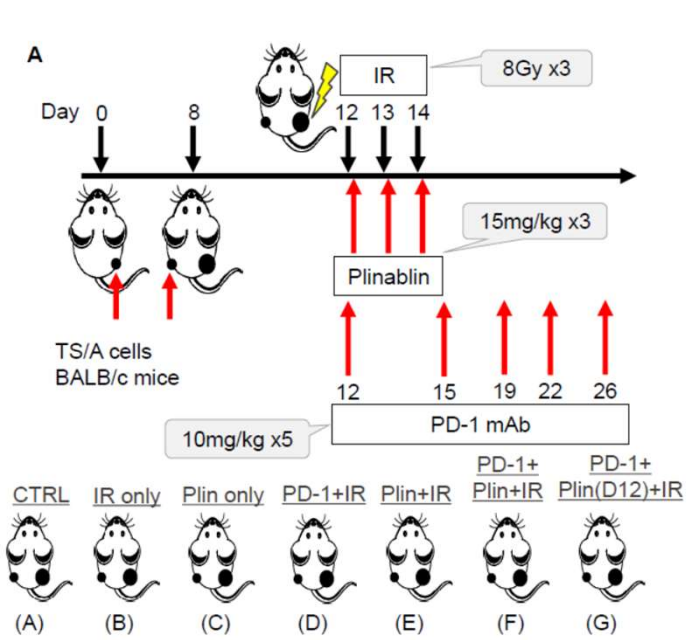
ARTICLE
Check for updates
https://doi.org/10.1038/s41467-020-18570-x OPEN

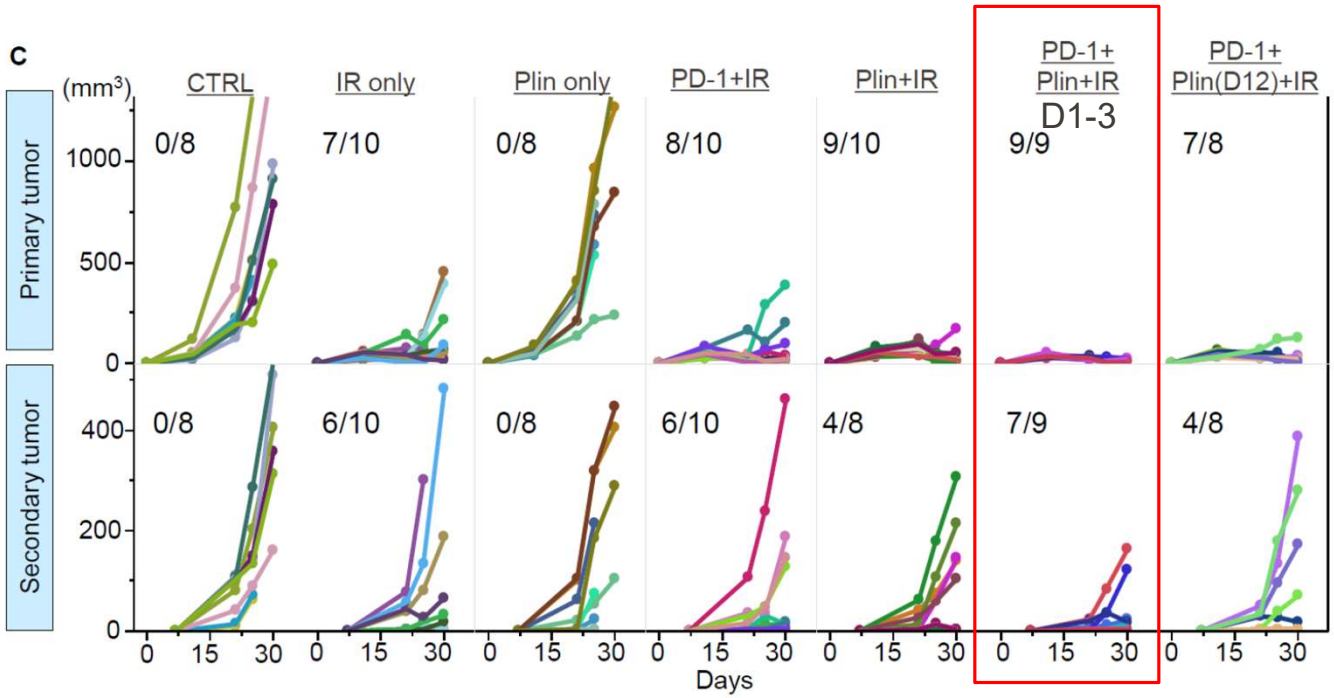
PD-L1 on dendritic cells attenuates T cell activation and regulates response to immune checkpoint blockade

Qi Peng[1,2], Xiangyan Qiu[3], Zihan Zhang[1], Silin Zhang[1], Yuanyuan Zhang[1], Yong Liang[3], Jingya Guo[4], Hua Peng[4], Mingyi Chen[3], Yang-Xin Fu[3] & Haidong Tang[1]✉

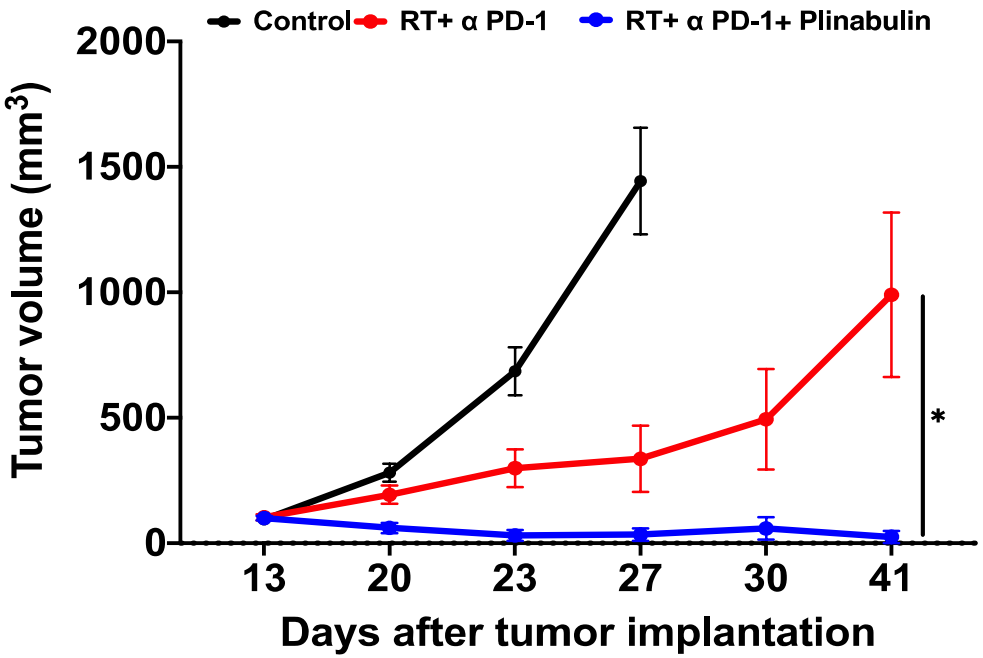
NATURE COMMUNICATIONS | (2020)11:4835 |

Triple combo (IR (8 Gy x 3) with plinabulin and IO) enhances primary tumor control and abscopal responses

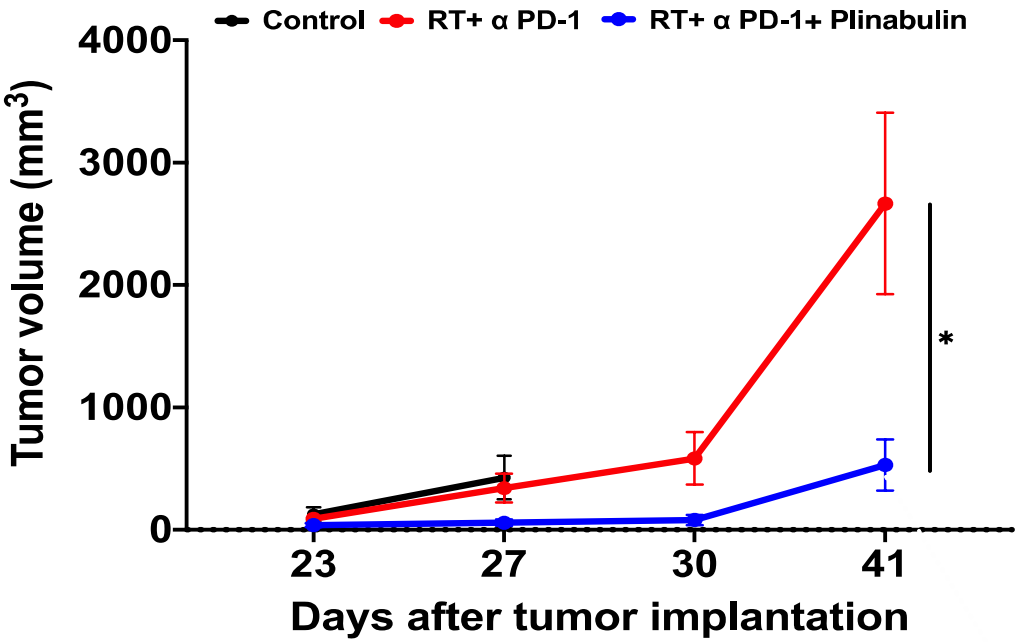




Triple combination enhances local and distant tumor control compared to RT+anti-PD-1

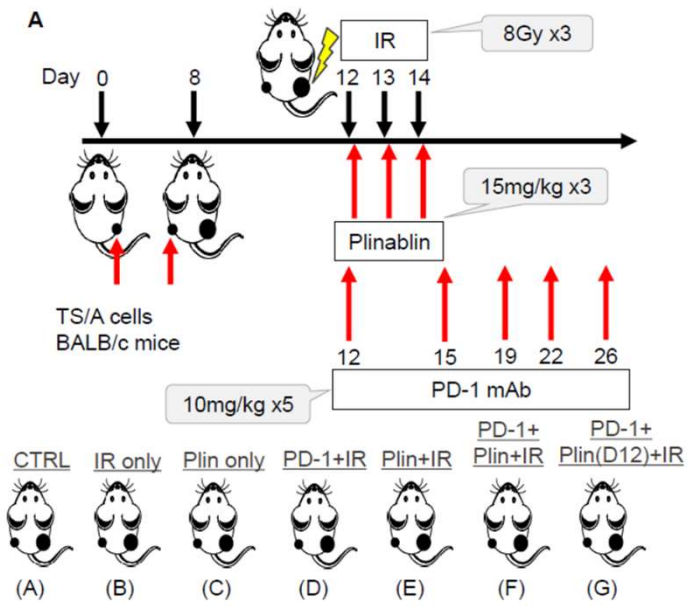


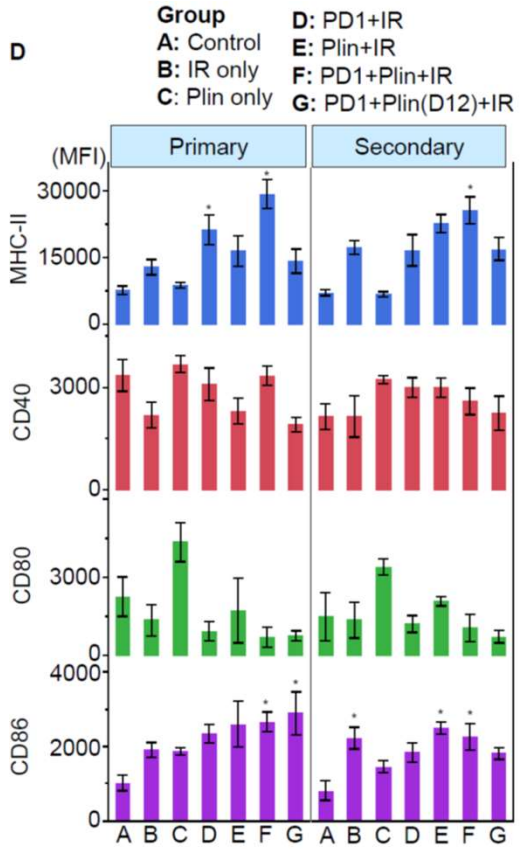
Primary tumor

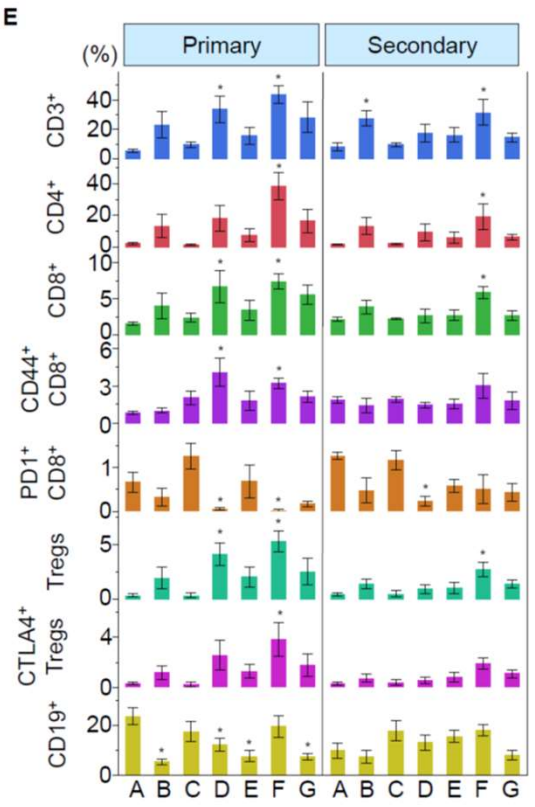


Abscopal tumor

Triple combo enhances immune stimulation in primary and abscopal sites







Working Hypothesis for the clinical trial

Taken together, these results suggest that “RT priming” followed by plinabulin and anti-PD-1/PD-L1 antibodies may have synergistic effect of stimulating the immune response (“Triple Combo” concept)

2020-0296: Phase 1b/2 study to evaluate safety of adding plinabulin + RT/IO in IO progressing solid tumors

Primary objectives:

- To assess safety and tolerability combining plinabulin with RT/IO in
- To assess ORR

Secondary objectives:

- To assess disease control rate (CR+PR+SD)
- To determine PFS
- To assess OS

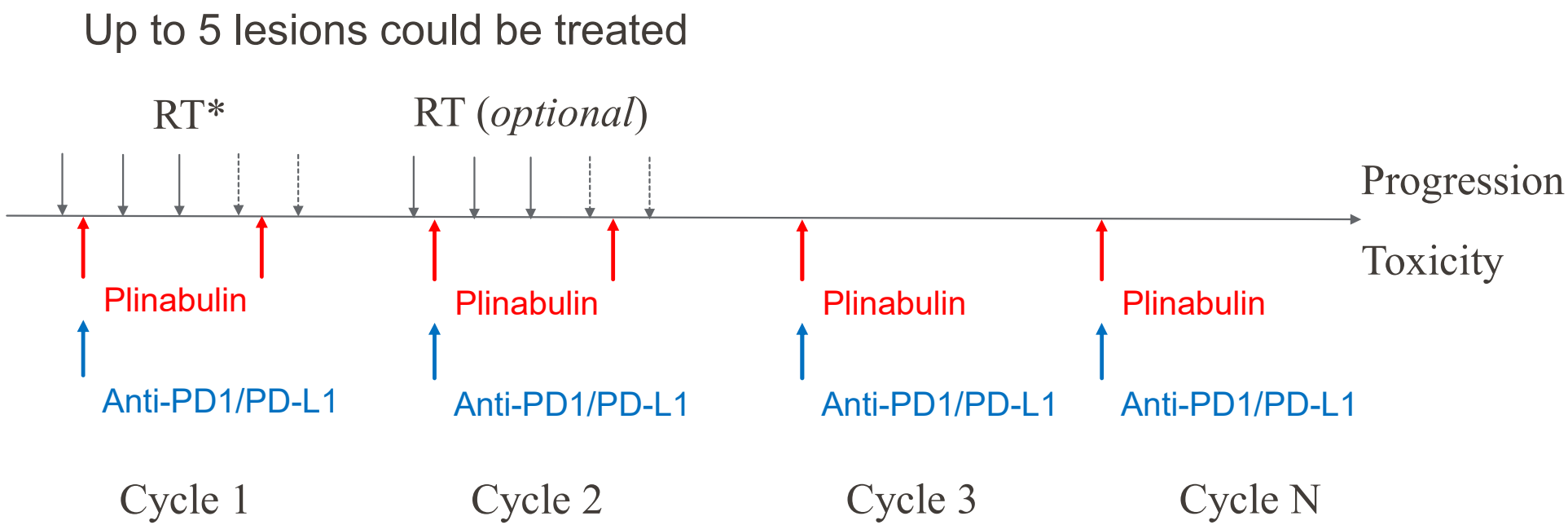
Exploratory Objectives

- TCR immune repertoire
- Single Cell RNAseq analysis on tumor samples
- Immune phenotyping from blood for multicolor flow cytometry
- Evaluate DC activation in the whole blood

Seven cancer types progressing on immunotherapy

- Bladder Cancer
- Melanoma
- Merkel Cell Cancer
- MSI-H Cancers (of any histology)
- Non-small cell lung cancer
- Small Cell Lung Cancer
- Renal Cell Cancer

Schema



* RT = 24 Gy/3 fx; 50 Gy/4 fx; 20 Gy/5 fx

Inclusion criteria

- Seven histologically or cytologically confirmed neoplasms that progressed on previous immunotherapies (anti-PD-1/PD-L1 +/- chemo or anti-CTLA4)
- At least one lesion is amendable for radiation
- At least one additional non-contiguous lesion that has not been irradiated amendable to radiographic evaluation
- Tissue biopsy using core needle biopsy must be obtained
- Age > 18 yrs
- ECOG 0-2
- Normal organ functions
- Life expectancy at least 12 weeks

Treatment protocol

All patients will receive RT (3-5 fractions) + plinabulin + anti-PD-1/PD-L1 (cycle 1) → plinabulin + anti-PD-1/PD-L1 mAb (cycle 2 and beyond until progression)

An optional sequential RT to other untreated lesions at the discretion of the treating radiation oncologist is allowed after cycle 1

Anti-PD-1/PD-L1 is the same as the regimen that was used at time of progression

Plinabulin dosing

Starting dose of plinabulin at 30 mg/m^2 IV on Day 1 and 4 in cycle 1 at the first day of radiation and the end of radiation

- If plinabulin is too toxic at 30 mg/m2, then option to go to 20 mg/m2 will be explored

Plinabulin is dosed 3-6 hours (but not greater than 12 hours) after RT

Plinabulin is administered IV over 60 minutes after anti-PD-1/PD-L1 mAb administration

Statistical considerations

Bayesian optimal interval (BOIN) design to find MTD on all comers

Two dose levels of 20 mg/m^2 and 30 mg/m^2, with 30 mg/m^2 at the starting level, by starting in cohorts of 3

Once MTD is determined up to 12 pts of all histologies, then additional 10 pts will be enrolled for both safety and efficacy in each of the seven cancer types to further define the safety of plinabulin dose for the RP2D, up to 70 subjects

Response evaluation will be based on the minimum of 5 subjects and up to 10 subjects per cohort. If the enrollment is very slow and cannot complete accrual at the time other cohorts are completed, then the cohort will close

Selection of disease cohort that will advance into phase 2 will be based on the cohort with the best response rate, which will be determined by the review committee

Phase 2

The histology and randomized design will be determined, for up to 102 pts randomized for the two arms

A maximum of 184 pts for this phase Ib/2 study

Translational studies

Tumor biopsy at pre-dose (<2 wks before RT) and post-dose (at 4th week for Q4wk or 6th week for Q3wk PD-1/PD-L1 regimen)

- TCR sequencing
- Single cell RNA sequencing

Whole blood samples at baseline and every 2 cycles:

- Immune profiling by multicolor flow cytometry
- TCR sequencing
- Dendritic cell activation
- Luminex cytokine assay
- ctDNA analysis

Trial status

- **Activated April 15, 2021**
- **Consented 5 pts (4 NSCLC, 1 RCC)**
- **2 had received the first cycle of triple combination therapy without SAEs**

Study-101 and DUBLIN-3

Trevor Feinstein MD

PIEDMONT
CANCER INSTITUTE

Treatment of advanced NSCLC, without a driver mutation

PIEDMONT CANCER INSTITUTE

Advanced NSCLC

Molecular testing with PD-L1

ECOG 0-1

- Adenocarcinoma
- Large cell
- Not otherwise specified

<u>PD-L1 expression positive > 50%</u>
- Pembrolizumab or another checkpoint inhibitor
- Platinum + pemetrexed + pembolizumab

Less commonly used
- Carboplatin + paclitaxel + bevacizumab and atezolizumab
- Nivolumab + ipilimumb +/- chemotherapy

<u>PD-L1 expression positive > 1-49%</u>
- Platinum + pemetrexed + pembolizumab

Less commonly used
- Carboplatin + paclitaxel + bevacizumab and atezolizumab
- Nivolumab + ipilimumb +/- chemotherapy

- Squamous cell

<u>PD-L1 expression positive > 50%</u>
- Pembrolizumab or another checkpoint inhibitor
- Carboplatin + taxane + pembolizumab

Less commonly used
- Nivolumab + ipilimumb +/- chemotherapy

<u>PD-L1 expression positive > 1-49%</u>
- Carboplatin + taxane + pembolizumab

Less commonly used
- Nivolumab + ipilimumb +/- chemotherapy

NSCLC

- Mortality from NSCLC is declining as a result of reduced incidence and survival-extending treatments in some regions, lung cancer remains a leading cause of cancer death worldwide. [1-3]
- Low survival rates for lung cancer are reflective of the large percentage of patients diagnosed with metastatic disease, wherein the 5-year relative survival rate is 6%. [3]
- Approximately 25% of patients do not receive treatment after being diagnosed with metastatic NSCLC[4,5]
- Of patients with advanced disease receiving first line treatment, about 30% will receive second line treatment[4,6]

1Howlader N, et al. *N Engl J Med. 2020;383:640-649. 2Bray F, et al. Ca Cancer J Clin. 2018;68:394-424. 3Siegel RL, et al. Ca Cancer J Clin. 2021;71:7-33. 4Simeone JC, et al. Future Oncol. 2019;15(30):3491-3502. 5Soares M, et al. BMC Pulm Med. 2020;20(1):240. 6Lester J, et al. BMC Cancer. 2021;21:515.*

Progression after a platinum chemotherapy and immunotherapy

- Non-squamous histology
  - Pemetrexed or docetaxel
  - Docetaxel plus ramucirumab
- Squamous histology
  - Docetaxel +/- ramucirumab

Docetaxel as standard of care after platinum progression

PIEDMONT CANCER INSTITUTE

- Prospective randomized trial of docetaxel versus best supportive care
- Performance statuses of 0 to 2
- Excluded with prior treatment of paclitaxel
- Randomized to docetaxel 100 mg/m^2 (49 patients) or 75 mg/m^2 (55 patients) or best supportive care.
- Six (7.1%) achieved partial responses (three patients at each dose level)
- Time to progression was longer for docetaxel patients than for best supportive care patients (10.6 *v* 6.7 weeks, respectively; $P < .001$)
- Median survival (7.0 *v* 4.6 months; log-rank test, $P = .047$).
- Increase toxicity of docetaxel 100 mg/m^2 compared to 75 mg/m^2

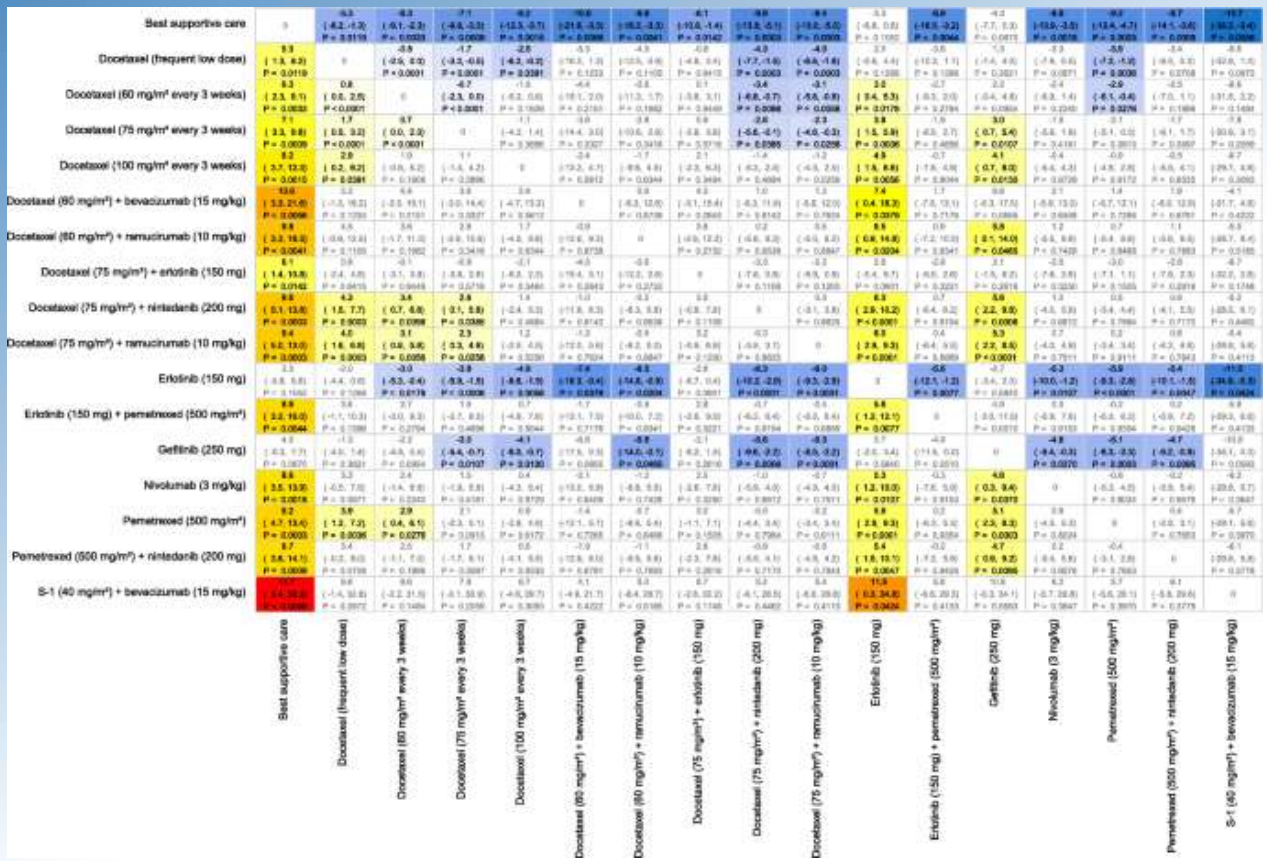
Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M, Burkes R, Coughlin S, Kim Y, Berille J. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000 May;18(10):2095-103. doi: 10.1200/JCO.2000.18.10.2095. PMID: 10811675.

REVEL: A randomized phase III trial of Ramucirumab plus docetaxel

- Ramucirumab, a recombinant human immunoglobulin G1 monoclonal antibody inhibiting vascular endothelial growth factor receptor-2
- 1253 patients with NSCLC were randomized to receive ramucirumab (10 mg/kg; n = 628) plus docetaxel (75 mg/m^2) or placebo plus docetaxel (n = 625) after disease progression on or after platinum-based therapy
- Overall survival was increased 10.5 months for ramucirumab-docetaxel and 9.1 months HR = 0.86 (95% CI: 0.75–0.98)
- Progression-free survival was also increased with the combination 4.5 versus 3 months; HR 0.76, 95% CI 0.68-0.86)
- Increased risk of bleeding, hypertension, intestinal perforation and arterial thrombus

Paz-Ares LG, Pérol M, Ciuleanu TE, Kowalyszyn RD, Reck M, Lewanski CR, Syrigos K, Arrieta O, Prabhash K, Park K, Pikiel J, Göksel T, Lee P, Zimmermann A, Carter GC, Alexandris E, Garon EB. Treatment outcomes by histology in REVEL: A randomized phase III trial of Ramucirumab plus docetaxel for advanced non-small cell lung cancer. Lung Cancer. 2017 Oct;112:126-133. doi: 10.1016/j.lungcan.2017.05.021. Epub 2017 Jun 3. PMID: 29191585.

“Heat map” mean OS times for non-squamous, EGFR Mutation negative, PD-L1 < 5%, after first-line treatment



Colors represent a “heat map” with blues representing large negative differences, increasing through to dark reds for large positive mean differences

Vickers, A.D., Winfree, K.B., Cuyun Carter, G. *et al.* Relative efficacy of interventions in the treatment of second-line non-small cell lung cancer: a systematic review and network meta-analysis. *BMC Cancer* **19,** 353 (2019). https://doi.org/10.1186/s12885-019-5569-5

21st century treatment for NSCLC

- In 1999, docetaxel was approved by the FDA for second line NSCLC
- Sadly, we have not made improvement
- We need treatment with improved:
  - Survival
  - Safety
  - Quality of life

Study 101 - Phase 1/2 Study of Vascular Disrupting Agent NPI-2358 + Docetaxel in Patients With Advanced Non-Small Cell Lung Cancer

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- Inclusion Criteria:
  - ECOG performance status ≤ 1
  - Pathologically or histologically confirmed advanced non-small cell lung cancer that has progressed after treatment with at least one chemotherapy regimen; measurable disease is not required for enrollment into this trial
  - Had received 1 or 2 prior treatments.
- Patients were randomly assigned to treatment with plinabulin plus docetaxel or docetaxel alone.
- Docetaxel was dosed at 75 mg/m^2 across all arms on day 1 of a 21-day cycle, and plinabulin (20 or 30 mg/m^2) was administered on days 1 and 8.

Study 101 - Phase 1/2 Study of Vascular Disrupting Agent NPI-2358 + Docetaxel in Patients With Advanced Non-Small Cell Lung Cancer

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- Primary Outcome Measures : Compare overall survival of patients treated with docetaxel to patients treated with docetaxel + NPI-2358
- Secondary endpoints were safety assessments, DOR, PFS and ORR
- PD-L1 tumor status was not characterized.

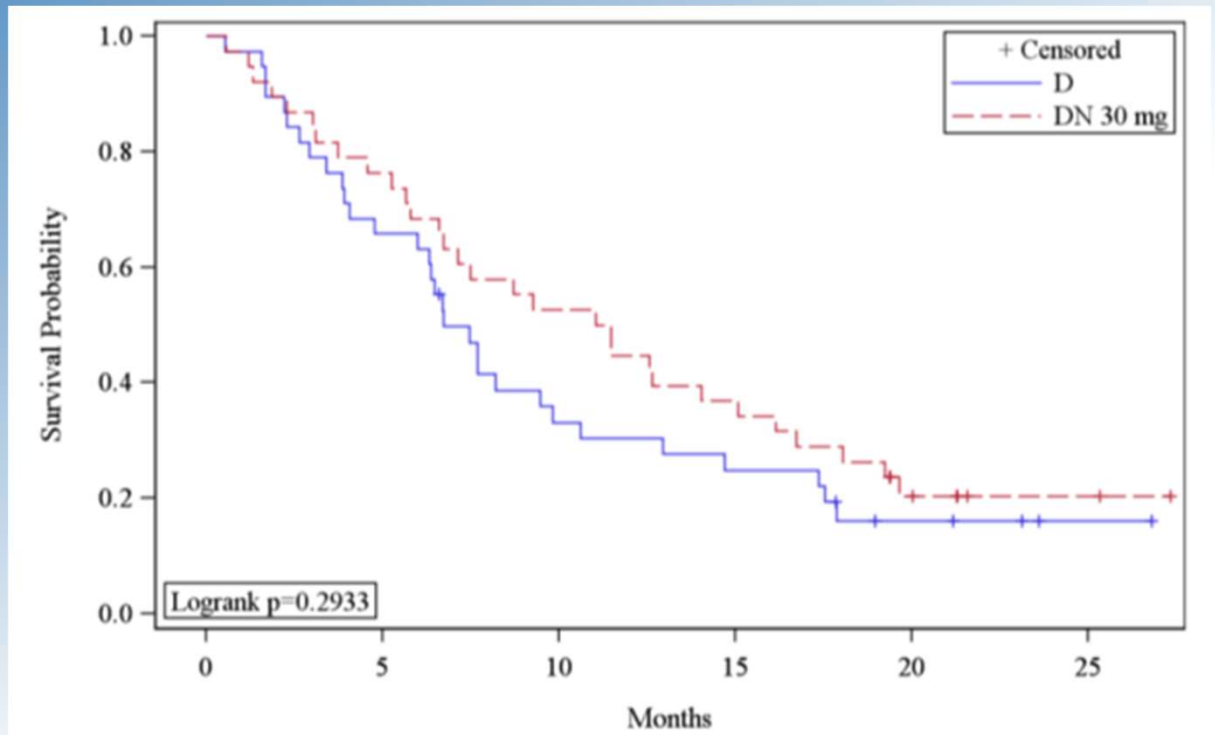
Study 101

- The 30 mg/m^2 Plin cohort was more effective than the 20 mg/m^2 cohort as an anticancer agent.
- Post hoc exploratory analyses were performed on phase 2 portion in the 30 mg/m^2 cohort, n=50 patients received 30 mg/m^2 Plin+ D and n=55 patients received D alone. 72% had measurable lung lesion.
- Response data in patients with a measurable disease

	mOS (months)	PFS (months)	OR%
Plin +Doc (n=38)	11.3	3.7	18.4
Doc (n=38)	6.7	2.9	10.5

Mohanlal RW, Lloyd K, Huang L, et al. Plinabulin as a novel small molecule clinical stage immuno-oncology agent for NSCLC. *J Clin Oncol.* 2017;35(suppl 7):139. doi:10.1200/JCO.2017.35.7_suppl.13

Phase 2 Study 101: Plinabulin has Anticancer Activity in NSCLC



	Subjects	Event	Censored	Median Survival	95% CL
D	38	31(82%)	7(18%)	6.733	(6, 9.833)
DN 30 mg	38	30(79%)	8(21%)	11.25	(6.733, 15.07)

- **Plinabulin MoA- targeted patients: Measurable lung lesion with RECIST 1.1 (CT scan > 1 cm in lung), which is around 70% of NSCLC**
- **Improved QoL and favorable Safety profile**

Study 101 Phase 2: Plinabulin has Superior Grade 4 Chemotherapy Induced Neutropenia Prevention vs 'Placebo'

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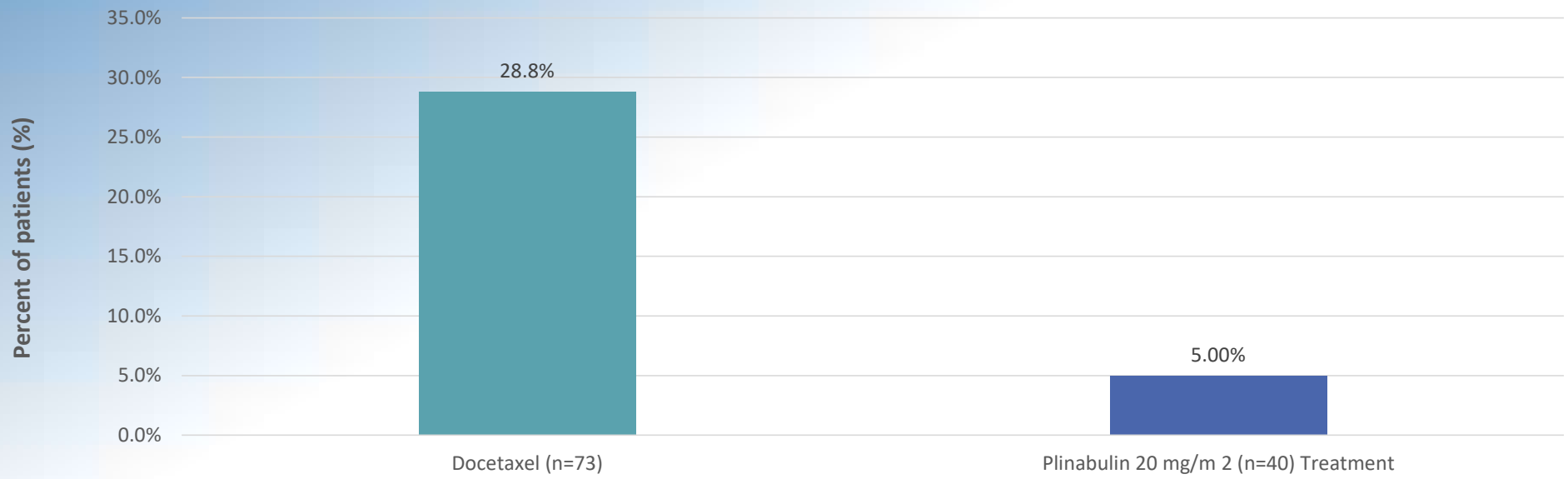
Incidence of neutropenia in patients treated with Docetaxel vs. Docetaxel + Plinabulin-20 mg/m2



Plinabulin appeared to protect against the development of docetaxel-induced neutropenia

- Reduced rates of sepsis (3.6% vs 0%, respectively)
- Severe infections (3.6% vs 0%, respectively)
- Docetaxel dose reductions due to toxicity (19.2% vs 6.7%, respectively)

Docetaxel + Plinabulin Compared to Docetaxel + Placebo in Patients With Advanced NSCLC (DUBLIN-3)

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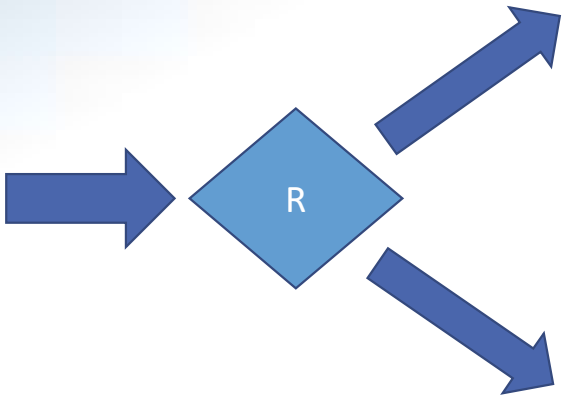
Global, single-blinded (blinding for patients only)
Stratified for region (Asia/non-Asia), and receiving 2nd- or 3rd-line systemic therapy with Docetaxel + Plinabulin or Docetaxel in a 1:1 ratio

- Non-squamous or squamous NSCLC
- ECOG performance status ≤ 2
- Progression during or after treatment with one or two treatment regimen
- Patients must have at least one measurable lung lesion
- OK for prior checkpoint inhibitor therapy



docetaxel + plinabulin

docetaxel + placebo

DUBLIN-3 (Study 103): Phase 3 in 2nd/3rd NSCLC, EGFR Wild Type

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Design

EGFR wild-type NSCLC (Pre-specified MOA target patients: Measurable lung lesion)

- Plinabulin + docetaxel vs docetaxel, 1:1 randomization, n=559 (fully enrolled)
- Approval possible with a single, qualified study
- Final analysis: at least 439 patient death events; study succeeds if $p < 0.046$ for Overall Survival, Expected Mid-Year 2021

Endpoints

Primary Endpoint: Overall Survival

Secondary Endpoints:

- ORR, PFS
- Percent of patients without severe neutropenia on Day 8 of Cycle 1
- Month 24 OS rate, Month 36 OS rate
- DoR
- Q-TWiST
- QoL
- Proportion of patients who received docetaxel >8 cycles, >10 cycles, and >12 cycles

- Secondary Endpoints go beyond OS
- Provide opportunity to demonstrate important benefits and address a range of unmet medical needs

Preliminary Data

- 2 successful interim analyses: DSMB recommended trial to continue without modification;
- Final look anticipated soon

Study Design

- Plinabulin 30 mg/m2 administered on Day 1 and Day 8 of each Cycle
- Docetaxel 75 mg/m2 is administered on Day 1 of each Cycle

Case Study 1

- 75 year old male smoker, 1.5 packs/day x 50 years with a history of severe mitral regurgitation
- January 8, 2015 PET/CT scan: 15 x 10 mm right middle lobe lung mass with hypermetabolic right hilar mediastinal in the left level IV cervical lymphadenopathy
- January 14, 2015 left cervical lymph node fine-needle aspirate: adenocarcinoma, positive for TTF-1, no EGFR, ALK or Ros1 mutation
- 2/17/2015 Carboplatin and pemetrexed followed maintenance pemetrexed × 14 cycles with disease progression
- April 2016 Nivolumab with progression after 27 cycles
- November 2016 brain metastases: whole brain radiation therapy
- 05/02/2017 Docetaxel + Plinabulin x 13 cycles with stable disease
- Discontinued the trial due to development of severe mitral valve insufficiency and heart failure. He declined to undergo cardiac surgery to repair his mitral valve

Case Study 1

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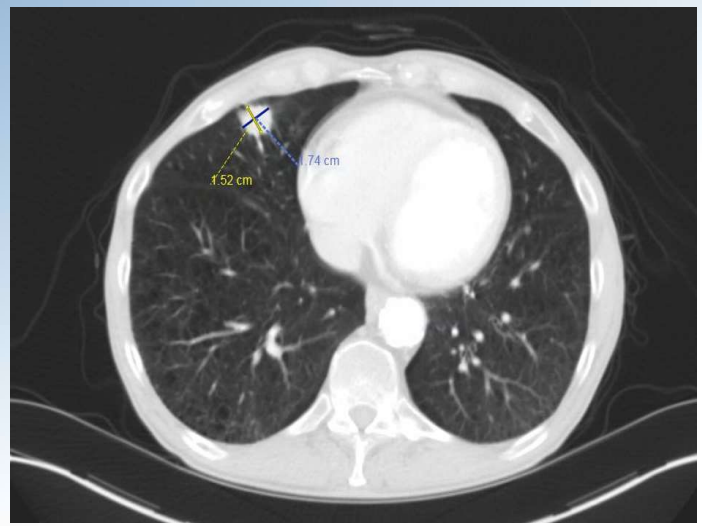
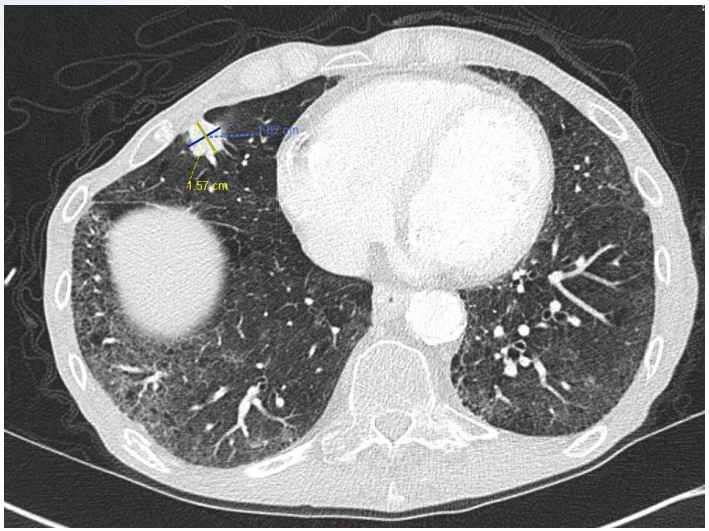
Before treatment



After 13 cycles

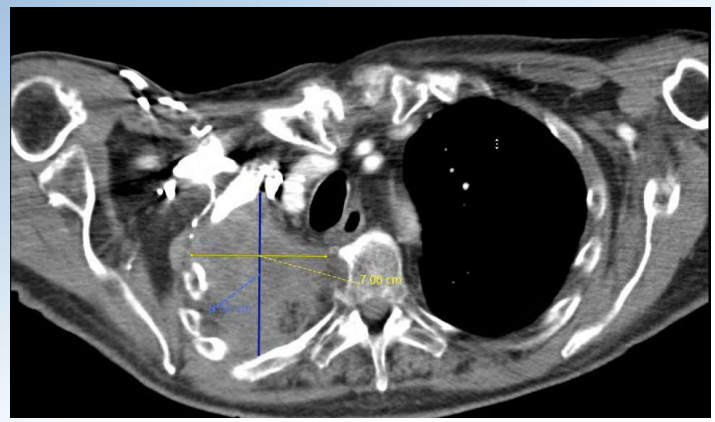


Case Study 2

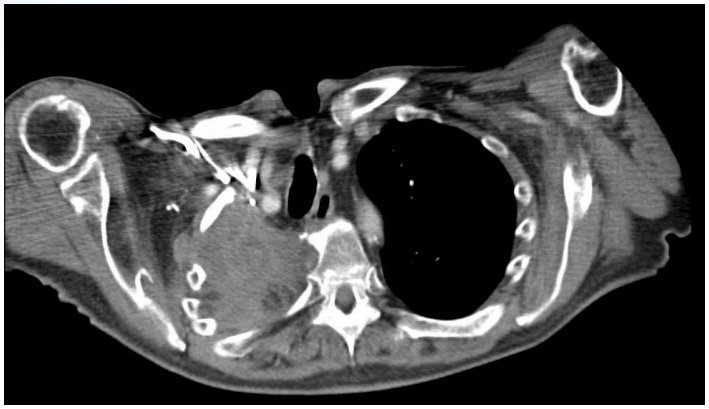
- 78 year old male with history of tobacco abuse and recurrent non-small cell lung cancer, squamous cell histology. He had a past medical history of GERD
- 09/24/16 robotic assisted right thoracotomy, right upper lobectomy converted to pneumonectomy and mediastinal lymph node dissection: right upper lobe poorly differentiate squamous cell carcinoma measuring 4.8 x 3.7 x 2.5 cm with no invasion into the visceral pleura. Metastatic disease to 2 of 3 parabronchial lymph nodes. Negative surgical margins after pneumonectomy. Lymphovascular invasion present. T2bN1. He was unable to undergo adjuvant treatment due to difficulty in recovery after pneumonectomy
- 12/27/2016 bronchoscopy: Mass noted at right bronchial stump, bronchial stump biopsy: invasive squamous cell carcinoma. No ALK or EGFR mutation. PD-L1 expression, 20%
- 1/11/2017 PET/CT scan: Interval development of right apical lung mass hypermetabolic with invasion into the ribs and tracheal wall. No evidence of distant metastatic disease
- 1/30/2017 carboplatin and paclitaxel with concomitant radiation therapy with progression
- 03/23/2017 Pembrolizumab with progression after 9 cycles
- 10/25/2017 Docetaxel + plinabulin × 2 cycles with stable disease, with treatment complicated by gastric perforation at gastic ulcer and atrial fibrillation.
- Last treatment of docetaxel + plinabulin was on 11/15/17 and no evidence of progression until September 2018

Case 2

10/20/2017



05/29/2018



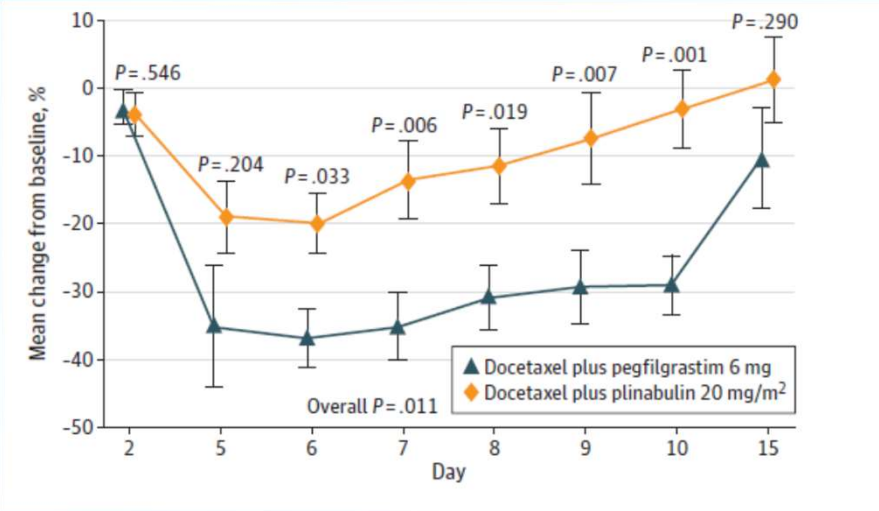
Supportive Data from CIN STUDY 105 in NSCLC

Efficacy of Plinabulin vs Pegfilgrastim in Adults with Non–Small Cell Lung Cancer

- Study BPI-2358-105 (NCT03102606): Phase 2/3, Multicenter, Randomized, Double Blind Study to Evaluate Duration of Severe Neutropenia with Plinabulin Versus Pegfilgrastim in Patients with Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy
- Advanced NSCLC after progression on platinum-based therapy
- Patients were randomly assigned to the following arms:
  - Arm 1: Docetaxel (75 mg/m2) + pegfilgrastim (6 mg) (N=14)
  - Arm 3: Docetaxel (75 mg/m2) + plinabulin (10 mg/m2) (N=13)
  - Arm 2: Docetaxel (75 mg/m2) + plinabulin (20 mg/m2) (N=14)
  - Arm 4: Docetaxel (75 mg/m2) + plinabulin (5 mg/m2) (N=14)
- ANC was assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 6, 7, 8, 9, 10, and 15

Blayney DW, Zhang Q, Feng J, et al. Efficacy of Plinabulin vs Pegfilgrastim for Prevention of Chemotherapy-Induced Neutropenia in Adults With Non–Small Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2020;6(11):e204429. doi:10.1001/jamaoncol.2020.4429

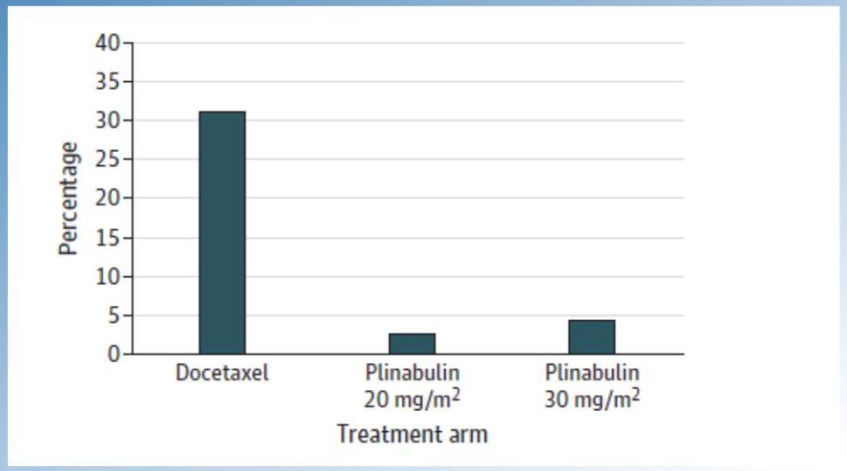
Less Thrombocytopenia with Plinabulin in comparison to Pegfilgrastim

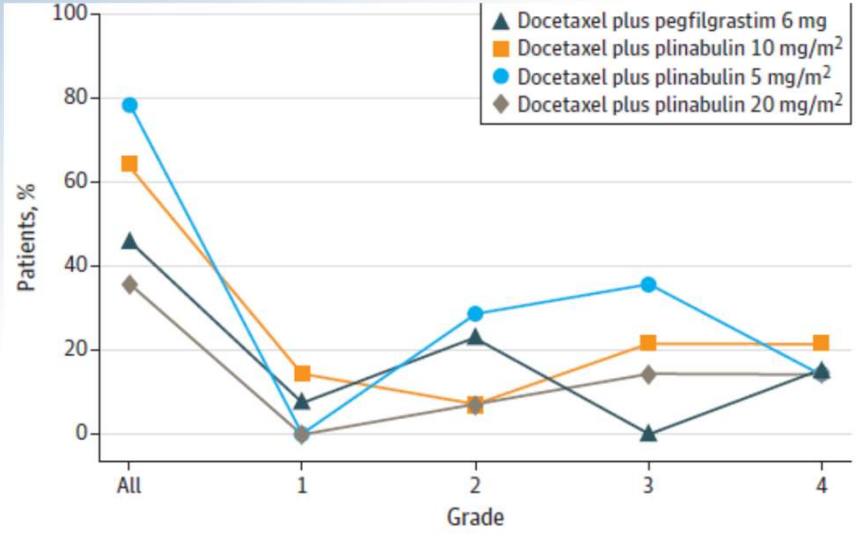


- Platelet counts by day during treatment cycle 1 expressed as percentage change from baseline
- No patients treated with plinabulin had thrombocytopenia of any grade, but 35% of patients treated with pegfilgrastim had at least grade 1 thrombocytopenia

Blayney DW, Zhang Q, Feng J, et al. Efficacy of Plinabulin vs Pegfilgrastim for Prevention of Chemotherapy-Induced Neutropenia in Adults With Non–Small Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2020;6(11):e204429. doi:10.1001/jamaoncol.2020.4429

Less Neutropenia with Plinabulin in comparison to Pegfilgrastim



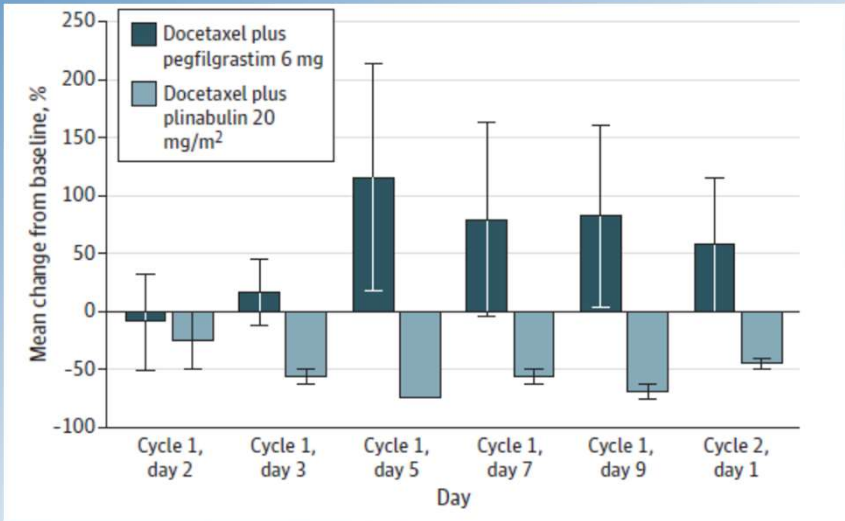


- In another phase 2 study of docetaxel for patients with NSCLC, patients were treated with plinabulin vs docetaxel alone.
- Grade 4 day 8 neutropenia developed in 2.6% of patients treated with plinabulin in contrast with 31% of patients treated with docetaxel alone

Percentage of treated patients against maximum neutrophil toxicity grade during treatment cycle 1

Blayney DW, Zhang Q, Feng J, et al. Efficacy of Plinabulin vs Pegfilgrastim for Prevention of Chemotherapy-Induced Neutropenia in Adults With Non–Small Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2020;6(11):e204429. doi:10.1001/jamaoncol.2020.4429

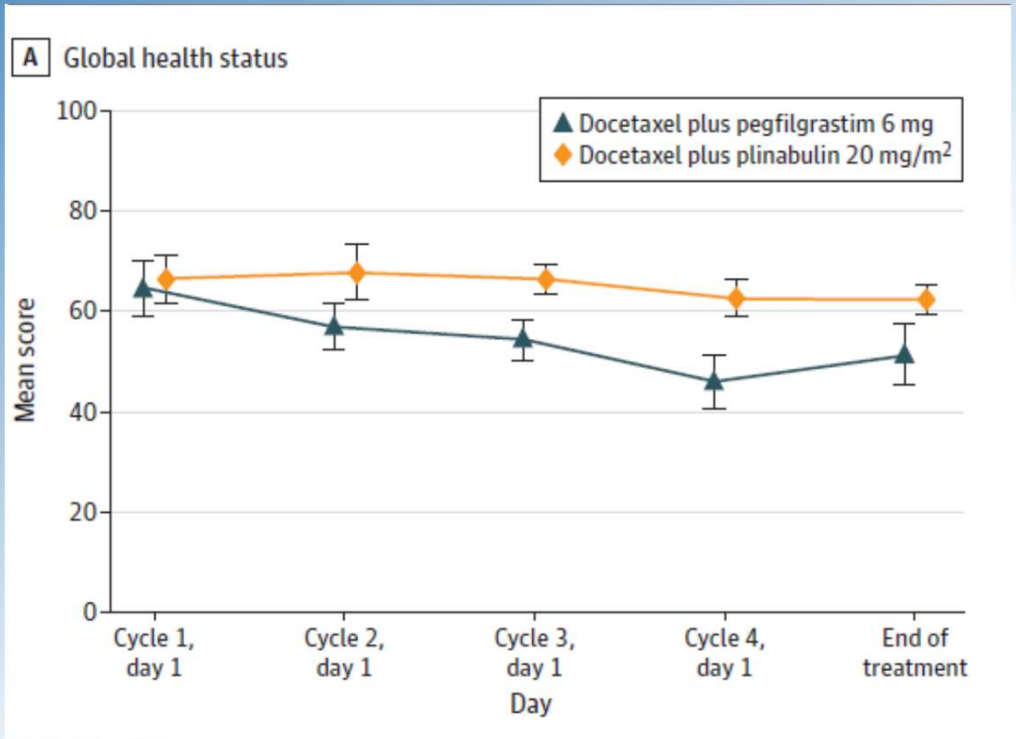
Less Bone pain with Plinabulin in comparison to Pegfilgrastim



- Bone pain is a known toxicity to Pegfilgrastim
- In patients who had no bone pain at study entry
  - Plinabulin treated patient had no bone pain after day 3
  - 35% of patients treated with pegfilgrastim reported bone pain
- Pegfilgrastim patients reported pain from day 3, which peaked on day 7 (90% change) before declining

Blayney DW, Zhang Q, Feng J, et al. Efficacy of Plinabulin vs Pegfilgrastim for Prevention of Chemotherapy-Induced Neutropenia in Adults With Non–Small Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2020;6(11):e204429. doi:10.1001/jamaoncol.2020.4429

Enhanced Quality of life with Plinabulin in comparison to Pegfilgrastim



- Plinabulin 20 mg/m2 showed a significant improvement in global health status (*P* < .001) vs pegfilgrastim
- Compared with their baseline state, patients treated with plinabulin 20mg/m2 significantly benefited in **fatigue** (*P* = .032), **pain** (*P* = .027) and **insomnia** (*P* = .05), compared with the symptomatic deterioration in patients treated with pegfilgrastim.

Blayney DW, Zhang Q, Feng J, et al. Efficacy of Plinabulin vs Pegfilgrastim for Prevention of Chemotherapy-Induced Neutropenia in Adults With Non–Small Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2020;6(11):e204429. doi:10.1001/jamaoncol.2020.4429

Target Product Profile

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Current Standard of Care	Plinabulin - Docetaxel Combination
• Modest survival benefit	• Potential survival benefit, with more long survivals due to GEF-H1 IO MOA
• Severe safety concerns, e.g. CIN	• Potential superior safety profile, including CIN reduction
• Poor Quality of Life	• Potential superior quality of life

BeyondSpring

Elizabeth Czerepak, CFO

BeyondSpring – Value Proposition

Committed to raising the standard of care for cancer patients, in the largest global markets, with first-in-class treatments that improve lives and clinical outcomes for millions of patients in need

BeyondSpring Value Proposition

Late-stage assets – Potential launch of Plinabulin in CIN early 2022
– Phase 3 (Dublin-3) data in NSCLC in mid 2021
– Triple combo IO trials underway; large potential

Large Markets – Broad label in CIN; solid tumors; IO combinations

Cost of Goods – Small molecule; Simple manufacturing process; Work with top CMOs

Broad and Long IP coverage – IP through 2036 in 36 jurisdictions

Global Capabilities – U.S. and China are two largest Rx markets

Cash Position at 3/31/21 - $90.6 million, sufficient for clinical and pre-launch costs

Headquarters – New York NASDAQ: BYSI

Recent Goals Achieved, Near Term Milestones for Value Creation

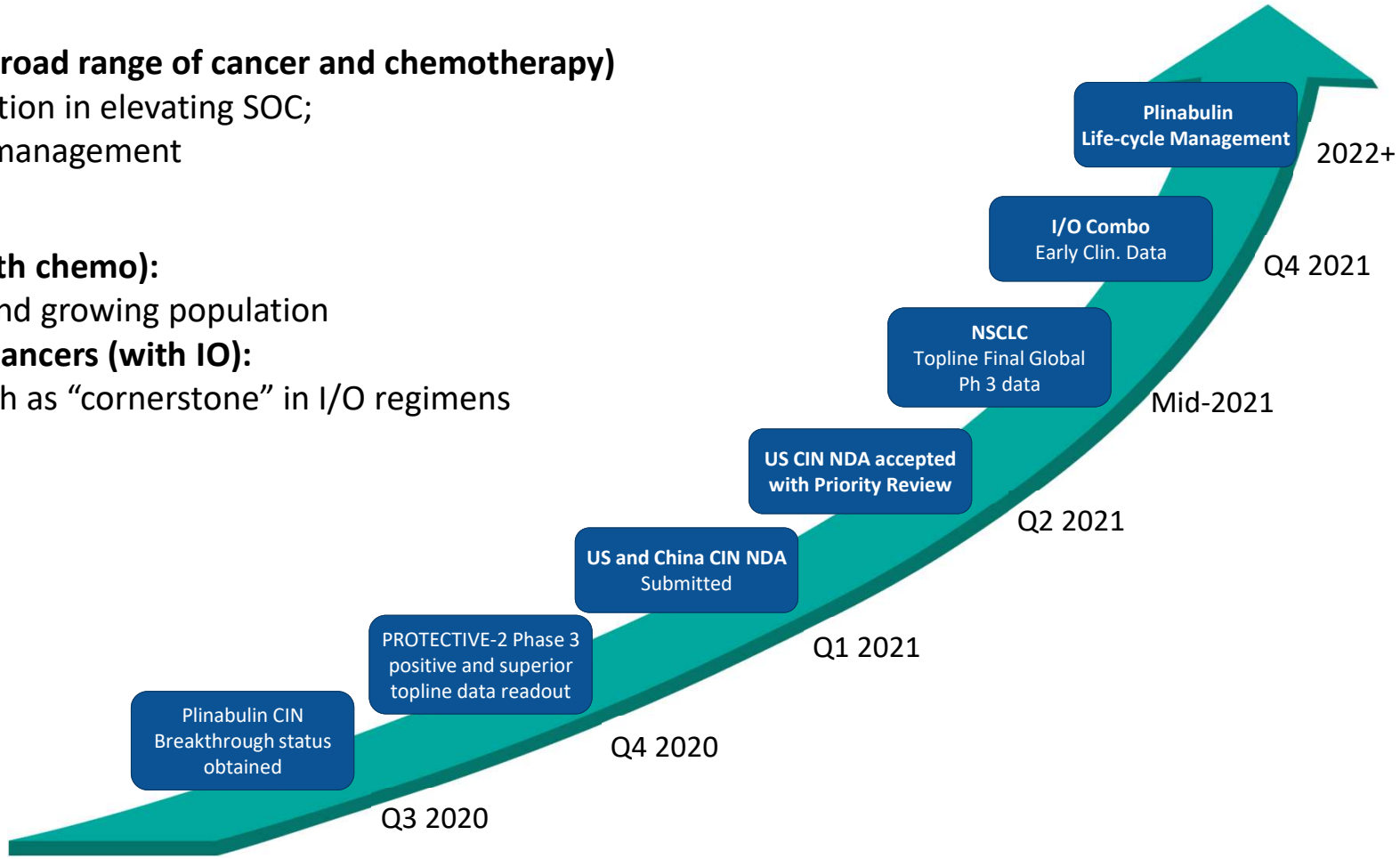
Plinabulin:

CIN (Targets broad range of cancer and chemotherapy)

- ✓ Value creation in elevating SOC;
- ✓ Life cycle management

Anti-cancer

- ✓ **NSCLC (with chemo):**
  - Large and growing population
- ✓ **Multiple Cancers (with IO):**
  - Establish as “cornerstone” in I/O regimens



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Questions?
Answers.