



**BeyondSpring**

## Plinabulin DUBLIN-3 NSCLC Topline Data



August 4 2021 | NASDAQ: BYSI

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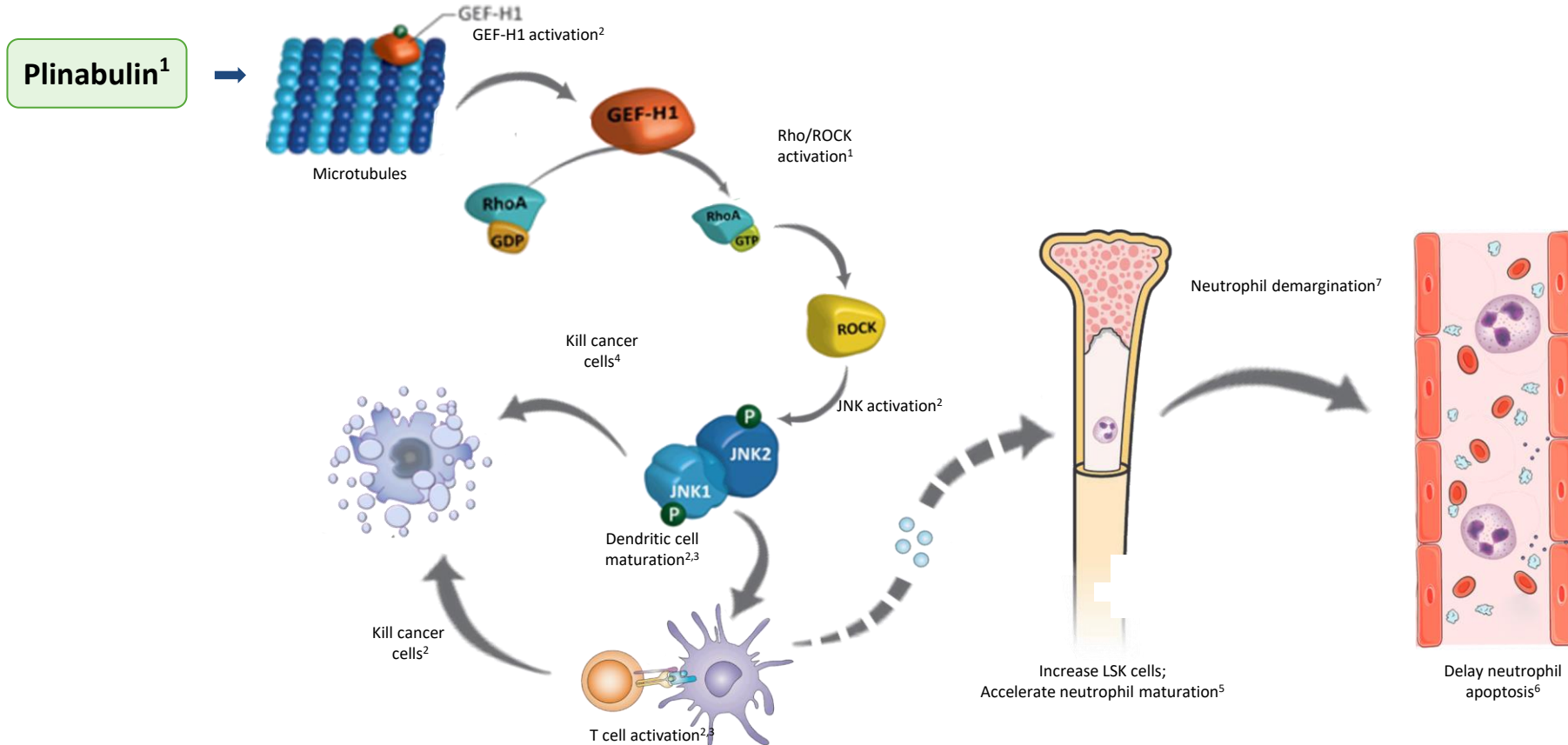
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# Plinabulin: First-in-Class, Selective Immunomodulating Microtubule-Binding Agent (SIMBA) - Potent Antigen Presenting Cell (APC) inducer



## Plinabulin Novel Target: Immune Defense Protein GEF-H1

**Chem** CellPress

Article  
Structure, Thermodynamics, and Kinetics of Plinabulin Binding to Two Tubulin Isotypes

**Kinetics** **Thermodynamics**  
Plinabulin selectivity  
 $\Delta\Delta G$   
 $\beta II$   
 $\beta III$

Authors: Giuseppina La Sala, Mariche Olsanic, Ashwini Sharma, José Fernando Diaz, Michel O. Steinmetz, Andrea Cavalli, nicola.zanarolo@unipi.it, g.la.sala@unipi.it

**HIGHLIGHTS**  
Plinabulin is a phase 3 anticancer and immunomodulating drug candidate.  
Plinabulin binding to tubulin differentiates it from other compounds.  
We report crystal structures of plinabulin in complex with  $\beta II$  and  $\beta III$  tubulin isotypes.  
We performed thermodynamic and kinetic studies on plinabulin selectivity and mechanism of action.

Plinabulin is a novel tubulin-binding agent that is currently in phase 3 clinical trials for cancer treatment and prevention of chemotherapy-induced neutropenia. Plinabulin binds within a distinct tubulin pocket, which differentiates it from other tubulin binders. Aimed at dissecting structural and energetic details of plinabulin binding to tubulin, we combine X-ray crystallography and computational modeling. We compare the plinabulin residence time with that of colchicine and combrestatine A4. Our study helps understand potential mechanisms underlying differential effects of this family of anti-tubulin drugs.

14 Oct 2019 | Chem | 5: 1-18  
November 20, 2019 | DOI: 10.26434/chemrxiv-2019-08-0277

**Cell Reports** Article

**GEF-H1 Signaling upon Microtubule Destabilization Is Required for Dendritic Cell Activation and Specific Anti-tumor Responses**

**Graphical Abstract**  
Immature DC → MDA → GEF-H1 → RhoA → JNK → MDA → Mature DC → CTL → tumor killing

Authors: Abhishek S. Kashyap, Laura Fernandez-Rodriguez, Yun Zhao, ..., Michel O. Steinmetz, Hans-Christian Reinacker, Alfred Zippelius

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**In Brief**  
Certain chemotherapeutics elicit potent anti-tumor immunity. Kashyap et al. demonstrate that microtubule-destabilizing chemotherapeutics induce maturation of dendritic cells through activation of microtubule-associated protein GEF-H1. This leads to effective priming of CD8 T cells against tumor antigens. GEF-H1 is critical for anti-tumor immunity of microtubule-targeting chemotherapy.

**Highlights**  
• Microtubule destabilization in dendritic cells drives DC maturation and T cell activation  
• GEF-H1 is released from microtubules, leading to its activation  
• GEF-H1 release triggers the RhoA-JNK-c-Jun signaling axis and AP-1 transcriptional response  
• GEF-H1 is critical for DC maturation, antigen cross-presentation, and anti-tumor immunity

Kashyap et al., 2019, Cell Reports 28, 3307-3320  
September 20, 2019 | DOI: 10.1016/j.celrep.2019.08.027

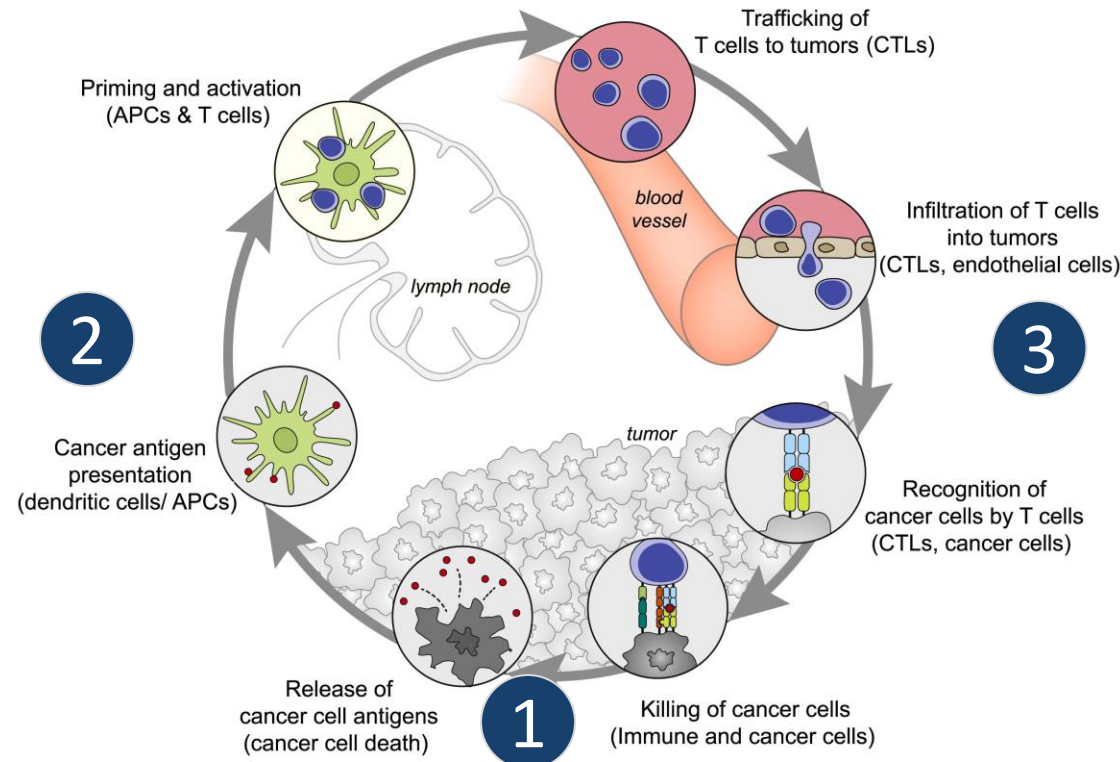
**CellPress**

# Plinabulin Induces Dendritic Cell Maturation (the most potent APC), a Key Step in Initiating Anti-cancer Durable Response

## 2 Plinabulin

Stimulate maturation of dendritic cells to increase antigen presentation

Dendritic cells are the most important antigen-presenting cells



1 Radiation/Chemotherapy/  
Plinabulin

**Release Tumor Antigens**

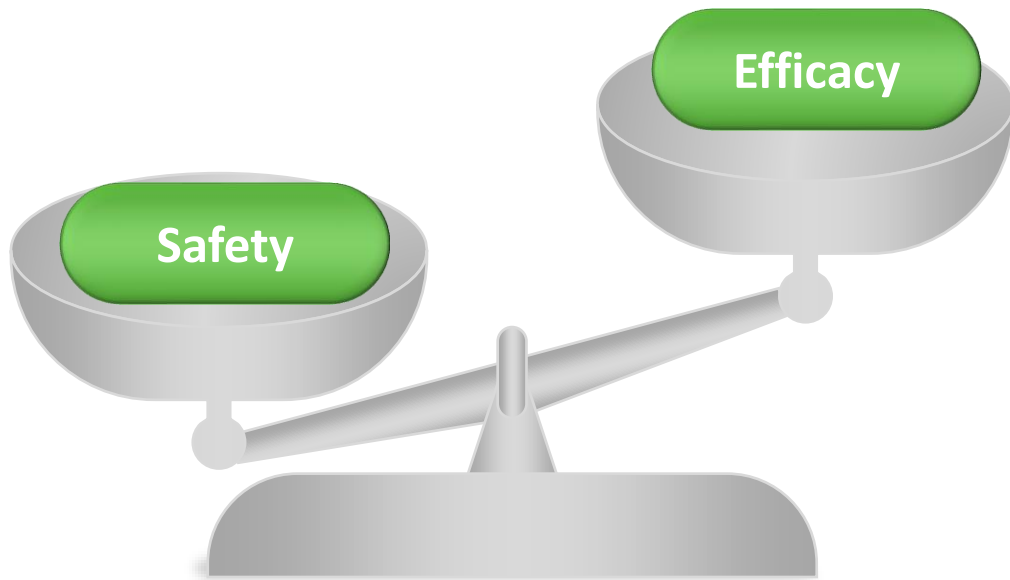
For more potent anti-cancer effect

3 Checkpoint Inhibitors

Optimize T cell response

1 + 2 + 3 → Optimal Immuno-Oncology Response

# Severely Unmet Medical Need – 2<sup>nd</sup>/3<sup>rd</sup> Line NSCLC, EGFR Wild Type



- Large patient population with limited treatment options
  - EGFR wild type: ~85% western NSCLC and ~70% of Asian NSCLC patients
  - With immunotherapies moved to first line, Docetaxel-based therapies are the mainstay therapy
  - TKIs are worse than docetaxel<sup>1</sup>
- Docetaxel-based Therapies (SOC)
  - Limited efficacy
  - >40% severe neutropenia

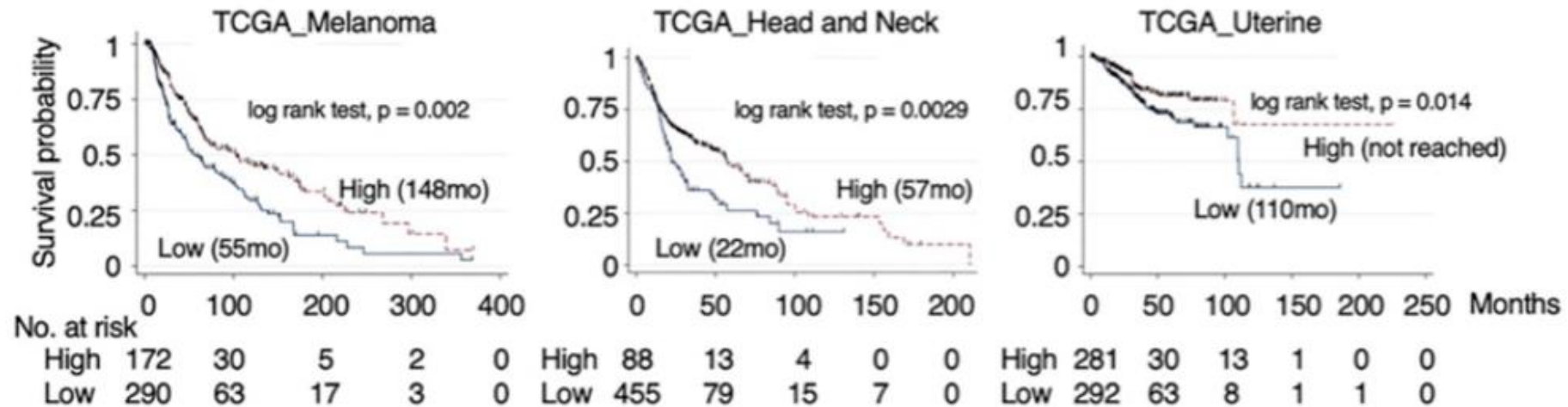
**Since nivolumab was approved 6 years ago, no new agent with novel mechanism has been approved in this indication.**



## Plinabulin Activates GEF-H1<sup>1</sup>

**Patients with High GEF-H1 Immune Signature Live Longer in Various Cancers<sup>1</sup>**

**Upper OS curve:** GEF-H1 immune signature high    **Lower OS curve:** GEF-H1 immune signature low



**Based on Plinabulin's Immune MOA, patients with measurable lung lesion were selected prospectively for Dublin-3 Study.**

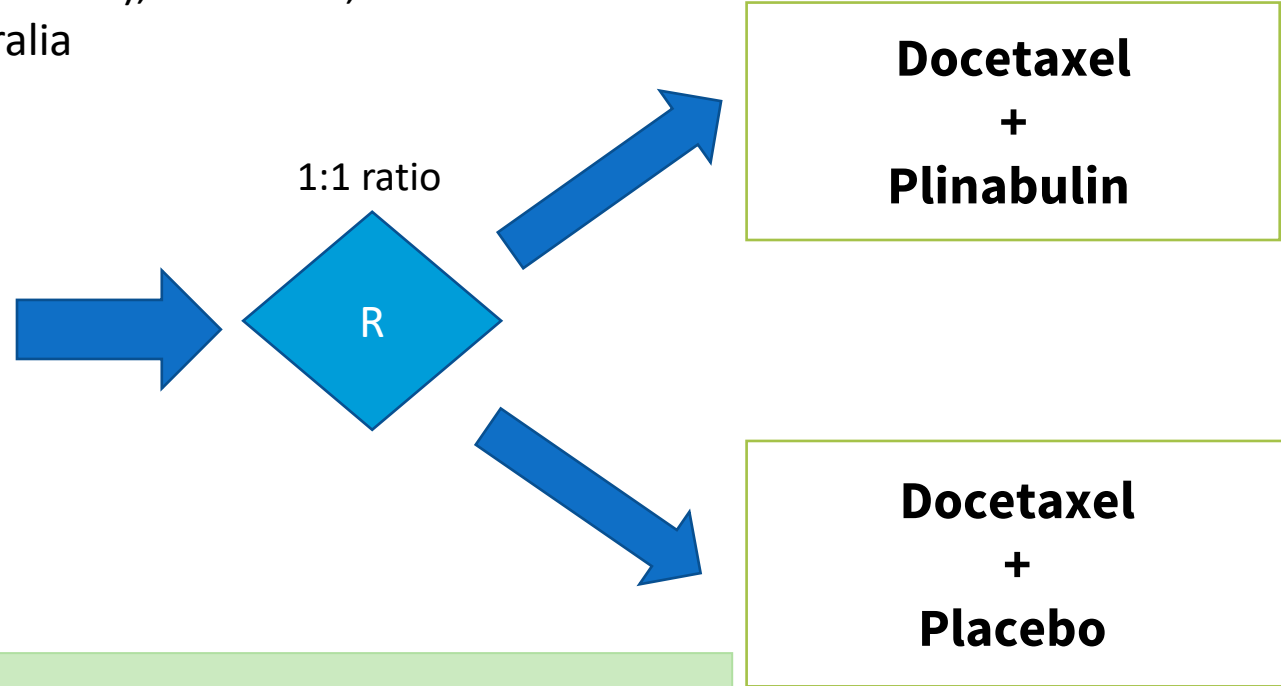


# Docetaxel + Plinabulin Compared to Docetaxel + Placebo in Patients With 2<sup>nd</sup>/3<sup>rd</sup> line NSCLC, EGFR wild type (DUBLIN-3)



Global, Randomized, Single-Blinded (blinding for patients only)  
Stratified for: Region (Asia/non-Asia), Prior Line, ECOG score  
60 sites: U.S., China, and Australia

- Non-squamous or squamous **NSCLC**
- Stage IIIb/IV
- ECOG performance status  $\leq 2$
- Progression during or after treatment with one or two treatment regimen containing platinum
- Must have at least one measurable lung lesion
- Prior checkpoint inhibitor therapy allowed



**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

# Dublin-3 Phase 3 Topline Data

- Significant Improvement in OS, PFS, ORR, 24 M, 36 M OS Rate (Combo vs. Docetaxel)
- Significant Reduction in Grade 4 Neutropenia (Combo vs. Docetaxel)

Primary Endpoint	Docetaxel (75 mg/m <sup>2</sup> ) N=281	Plinabulin (30 mg/m <sup>2</sup> ) + Docetaxel (75 mg/m <sup>2</sup> ) N=278
OS (months or M)		Mean OS, p=0.03 OS Log-rank p<0.04

**Doubling OS rate in 24 M, 36 M, and 10.6% >48 M OS rate – Plinabulin Immune Durable Anti-cancer Benefit**

Secondary Endpoint - Hierarchy Order	Docetaxel N=281	Plinabulin (30 mg/m <sup>2</sup> ) + Docetaxel (75 mg/m <sup>2</sup> ) N=278
ORR (%)		P <0.03
PFS (months or M)		P<0.01
Grade 4 neutropenia, cycle 1 Day 8 (%)	27.8%	5.3%; p<0.0001
24 Month OS Rate (%)	12.5%	22.1%; p<0.01
36 Month OS Rate (%)	5.3%	11.7%; p<0.04
48 Month OS Rate (%) - exploratory	0%	10.6%; p value cannot be calculated



# Product Profile (Plinabulin + Docetaxel for 2<sup>nd</sup>/3<sup>rd</sup> line NSCLC, EGFR wild type)

Next steps: Discuss filing plan with FDA & NMPA in 2021 with potential filing 1H 2022

## Docetaxel (Current SOC)

- Modest survival benefit
- Severe safety concerns, e.g., CIN
- Poor Quality of Life

## Plinabulin - Docetaxel Combination

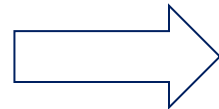
- Survival benefit, with longer survival due to GEF-H1 I/O MOA
- Favorable safety profile, including significant CIN reduction
- Improved quality of life

- **Lower Grade 4 AE frequency and a shift to lower grade AE**
- **No unexpected AE concerns were identified**

# Plinabulin: potential as the “Cornerstone” Therapy to Add onto Current IO Therapies to Address Severe Unmet Medical Needs



PD-1/PD-L1 Inhibitors  
- \$30 B global annual sales

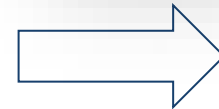


Potential to greatly expand  
the addressable market

## Current Severe Unmet Medical Needs

- PD-1/PD-L1 resistant patients need later line therapies
- PD-1 + chemo double efficacy of PD-1, but with CIN risk
- PD-1 or PD-1+CTLA-4 with high ir-SAE
- PD-1/PD-L1 non-responsive tumor;
- Patients who cannot use PD-1/PD-L1

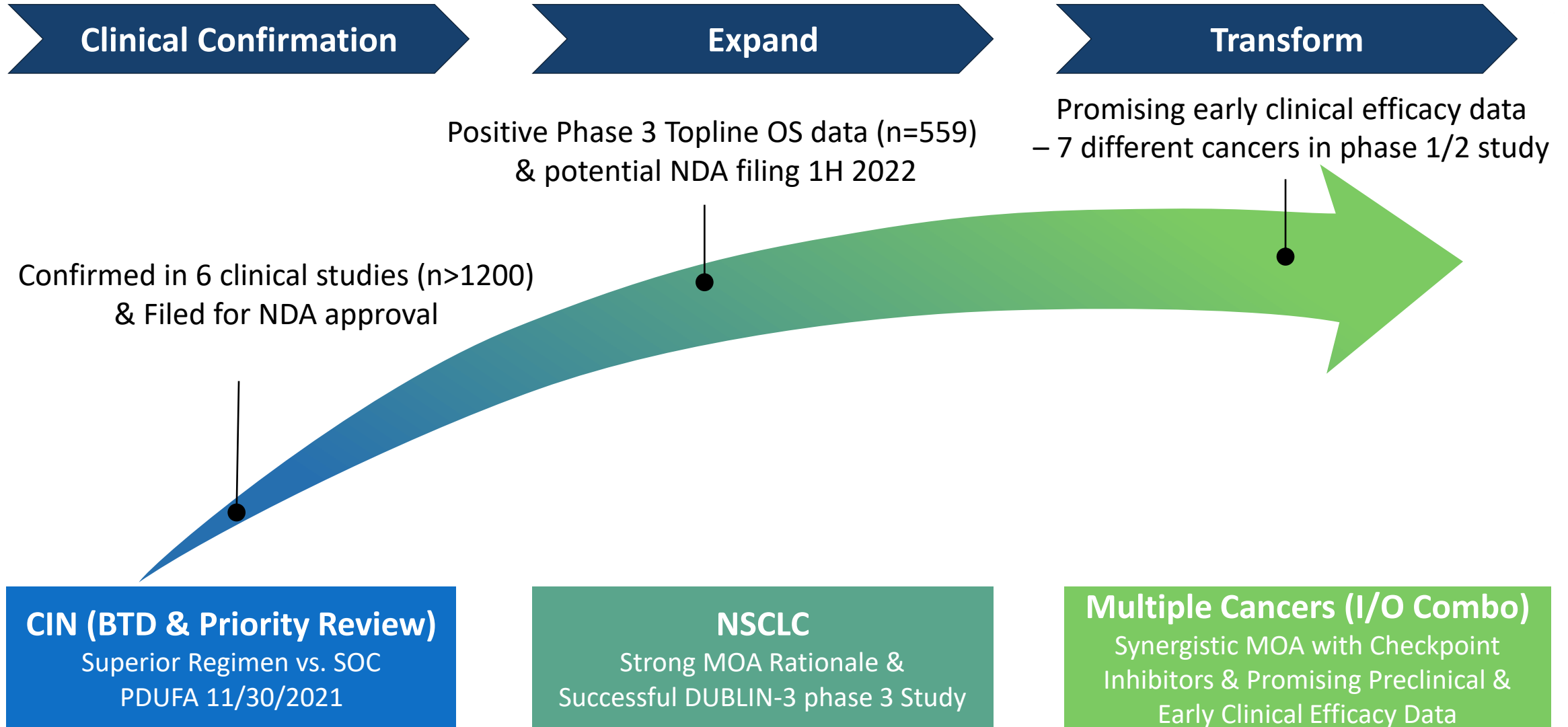
+“Easy-  
to-use”  
APC  
Inducer



## Plinabulin Clinical Development

- Plinabulin + I/O + chemo/radiation
- Plinabulin is developed as a CIN prevention agent (pan cancer, pan chemo)
- Plinabulin+PD-1+CTLA-4 in SCLC
- Plinabulin+ I/O + chemo/radiation
- Plinabulin + chemo

# Plinabulin Franchise: Pipeline in a Drug





thank you!

[www.beyondspringpharma.com](http://www.beyondspringpharma.com)