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BeyondSpring

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Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons why actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

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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.

Investment Highlights

Plinabulin Favorable Safety Profile	**> 700 Cancer Patients** Treated with Good Tolerability
Anti-cancer Efficacy	Positive Phase 3 study in 2L/3L NSCLC with Significant Overall Survival Benefit: 1. durable anti-cancer benefit in doubling 2-year, 3-year OS rate 2. enables more chemo doses by reducing chemotherapy-associated TRAE
Target IO Failure	Promising efficacy data in triple IO combo (Plinabulin + PD-1/PD-L1 + radiation/chemotherapy) in patients with various cancers after IO-failure
SEED: Novel TPD Platform & Pipeline	SEED: 9 Disclosed Pipeline Assets with 1 expected to enter First Human Dose in 2025; Investments and R&D Collaborations from Eli Lilly and Company and Eisai
Intellectual Property	Strong Global Patent Protection: granted/allowed patent to 2038 in 48 jurisdictions, including US, EU, Japan, and China
Regulatory Strategy	Multiple Phase 1/2 studies reading out in 2024 that will inform potentially pivotal randomized clinical studies beginning in 2025

Pipeline

	Indication/Target	Program	Preclinical	Phase 1	Phase 2	Phase 3	Registration	Trial Name / Collaborator
Late stage	**NSCLC (2nd/3rd line)**	Plinabulin + Docetaxel						Study 103 (DUBLIN-3) - Presented at ISLAC, ESMO 2024 Published in "LANCET Respiratory Medicine" 09/2024
Late stage	**CIN Prevention**	Plinabulin + Pegfilgrastim						Studies 105 & 106 (PROTECTIVE-1 & PROTECTIVE-2)
Investigator Initiated Trials	**ES-SCLC (2nd/3rd line)**	Plinabulin + Nivolumab + Ipilimumab						Presented at SITC 2023
Investigator Initiated Trials	**NSCLC (2nd/3rd line PD-1/L1 progressed)**	Plinabulin + Pembrolizumab + Docetaxel						Study 303 Presented at ESMO 2024, SITC 2024
Investigator Initiated Trials	**ES-SCLC (1st line)**	Plinabulin + Pembrolizumab + Etoposide / Platinum						Study 302
Investigator Initiated Trials	**Multiple cancers (PD-1/PD-L1 failed)**	Plinabulin + PD-1/PD-L1 + Radiation						Presented at SITC 2023
Early Stage	**Preclinical assets**	BPI-002, BPI-003, BPI-004						
SEED	**9 Targets in Oncology, Neurodegeneration, Immunology and Antiviral**	Targeted Protein Degradation Molecular Glue Platform						

1) Dalian Wanchunbulin Pharmaceuticals Ltd., a BeyondSpring subsidiary, owns Greater China rights to Plinabulin
2) BeyondSpring is an equity investor of SEED Therapeutics, a targeted protein degradation company

Sale of a Portion of Equity Interest in SEED to Advance Lead Asset Plinabulin in Anti-Cancer Clinical Development

- **$35.4 M gross proceeds for non-diluting financing by selling a portion of SEED A-1 shares**
  - Strategically positioned to advance our 303 and 302 Studies in Plinabulin combination with immune checkpoint inhibitors to registrational trials
  - Explore business development partnerships to bring Plinabulin to cancer patients with limited treatment options

- **Win-win for both BeyondSpring and SEED**
  - BeyondSpring will be strategically positioned to advance its late-stage clinical trials for Plinabulin without diluting shareholder equity.
  - BeyondSpring will retain 14.4% equity stake in SEED and remain part of SEED's continued success in revolutionizing drug discovery.
  - SEED will diversify its shareholder base while continue to drive success in Targeted Protein Degradation innovation.

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Plinabulin: First-in-class Late-Stage Clinical Asset for Cancer Treatment

First-in-class Asset: Plinabulin

Anti-cancer Clinical Agent	• Positive Phase 3 study in 2L/3L NSCLC, successfully demonstrated significant OS benefit, doubling 2-year, 3-year OS rate – proving plinabulin's clinical utility
Target IO Failure Severe Unmet Needs	• Promising efficacy data in triple IO combo (Plinabulin + PD-1/PD-L1 + radiation/chemotherapy) in patients with various cancers after IO-failure
Favorable Safety Profile	• Small molecule with novel chemical structure; 700+ Cancer Patients Treated with monotherapy or combination with Good Tolerability
Ease of Use	• Intravenous (IV) Infusion: 1 or 2 doses per cycle
Strong Global Patent Protection	• Granted/allowed patent to 2038 in 48 jurisdictions, including the US, EU, Japan and China

Plinabulin: Addressing Severe Unmet Medical Needs as an Add-on Therapy to Immuno-Oncology Regimens

PD-1/PD-L1 Inhibitors
$50B global annual sales

→ Potential to greatly expand the addressable market

Current Severe Unmet Medical Needs

2L/3L: PD-1/PD-L1 relapsed/refractory patients

1L: PD-1/PD-L1 + chemo doubles anti-cancer efficacy of PD-1, but with CIN risk

"Cold" Tumor: PD-1/PD-L1 non-responsive tumor

Plinabulin:
APC Inducer with easy IV administration →

Plinabulin Clinical Development

Re-sensitize: Plinabulin + PD-1/PD-L1 + chemo/radiation/ADC

Increase Combo Anti-cancer Efficacy: Plinabulin + PD-1/PD-L1 + chemo/ADC

Turn "cold" into "hot" Responding Tumor: Plinabulin+ PD-1/PD-L1 + chemo/ADC; Plinabulin + chemo/ADC

The global cancer immunotherapy market exceeds **$50 billion annually**. Plinabulin has the potential to address the unmet medical needs of the **60% of I/O patients who develop resistance**.

Plinabulin's Journey: Development Milestones Across 700+ Cancer Patients

Phase 1a, 1b Study
(Clin Cancer Res 2010; Invest New Drugs 2012)
- Initiation 2006

Plinabulin MOA Discovery: Unique Tubulin Binder, Induces DC Maturation
(Chem 2019; Cell Reports 2019)
- Elucidated in Collaboration with MD Anderson (AACR 2020), Mass General, and University of Basel

Dublin-3 Anti-Cancer Study
(Lancet Respiratory Medicine 2024; ISLAC 2024; ESMO 2024)
Phase 3 in 2L/3L NSCLC, EGFR wild type
- First patient enrolled in 11/2015
- Plinabulin + Docetaxel vs Docetaxel with significant OS benefit (n=559, HR=0.82)

2006 - 2010 | **2011 - 2015** | **2016 – 2020** | **2021 - 2025**

Phase 2 Study (ASCO 2014)
- Initiation 2009

Reduce Chemotherapy-Induced Neutropenia:
Phase 2/3 studies as monotherapy, or G-CSF combination (JAMA Oncology 2020; JAMA Network 2022)
- First patient enrolled in 04/2017

PD-1/PD-L1 Failed Patients
- Triple IO combination with PD-1 and chemo/radiation
- 303 Study (2L/3L NSCLC): 21% ORR, 89% DCR, mPFS 8.6 months (ESMO 2024, SITC 2024)
- MD Anderson phase 1: DC maturation MOA validated in responding patients; Patient selection criteria based on GEF-H1 (SITC 2023; Paper in Review)

Plinabulin is a Reversible Tubulin Binder with Differential Binding, Clinical Activity and Favorable Safety Profile

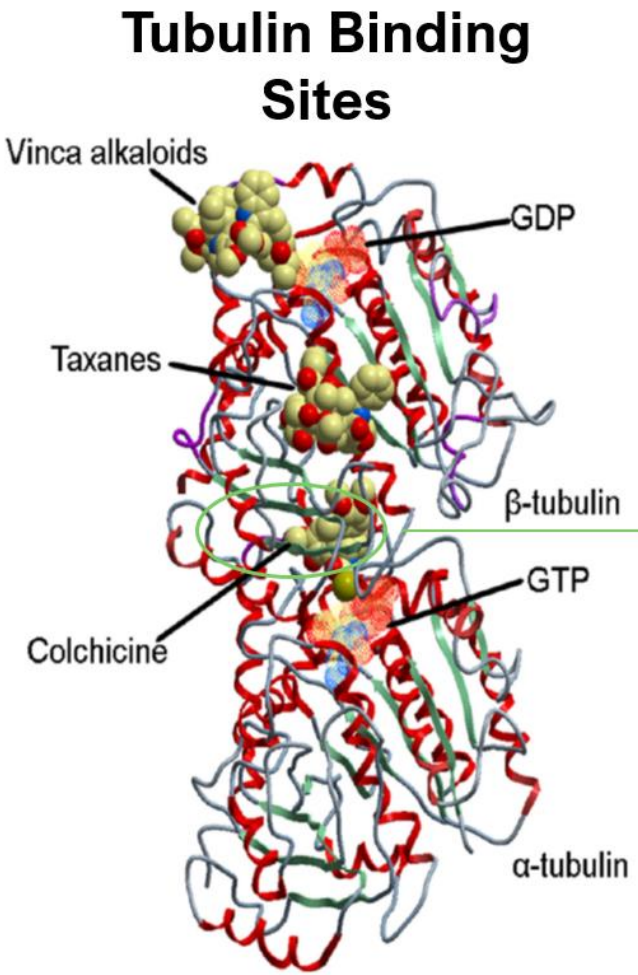
Plinabulin is a reversible tubulin binder and does not alter tubulin dynamics

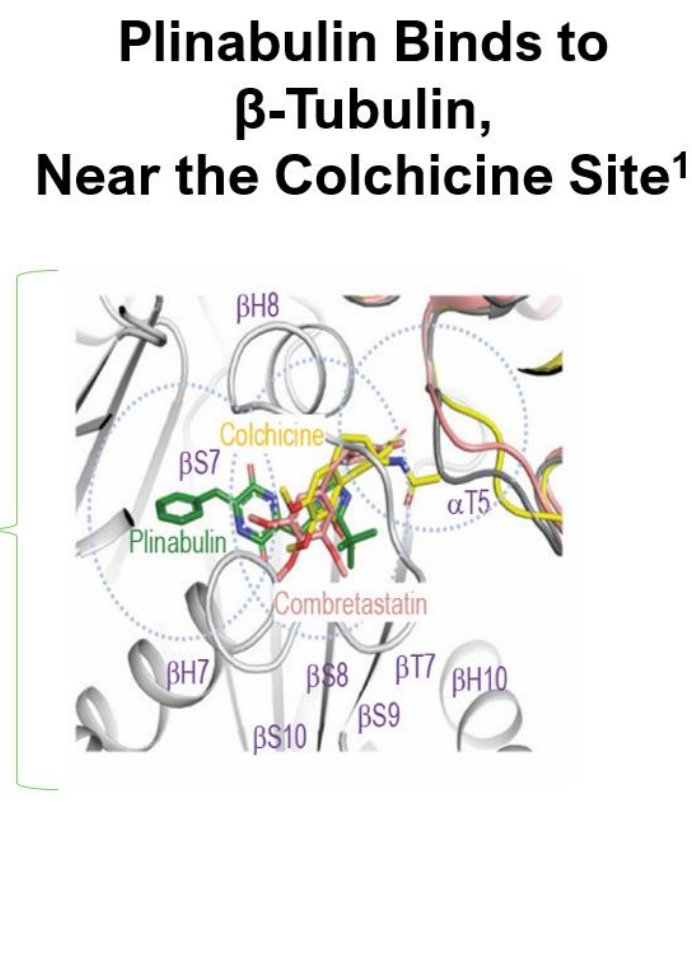
Conventional tubulin binding agents (such as taxanes, vinca alkaloids, and colchicine) alter tubulin dynamics upon binding, resulting in neutropenia and cardiac side effects.

Plinabulin's tubulin binding site is distinct from that of these other agents (first in class). Because **binding is reversible**, plinabulin does not change tubulin dynamics.

Consequently, **plinabulin exhibits a favorable safety profile**, differentiating it clinically from other tubulin binding agents with concerning side effects that restrict their clinical utility.

- ✓ Side effects include transient hypertension (target vasculature) and GI side effects.
- ✓ Phase 1a study: At phase 3 dose, 77% patients had tumor blood flow decrease >20% based on DCE-MRI data[2].





[1] La Sala et al., 2019 Chem 5(11): 2969-2986
2. Mita et al. 2010 Clini Cancer Res 16: 5892-5899

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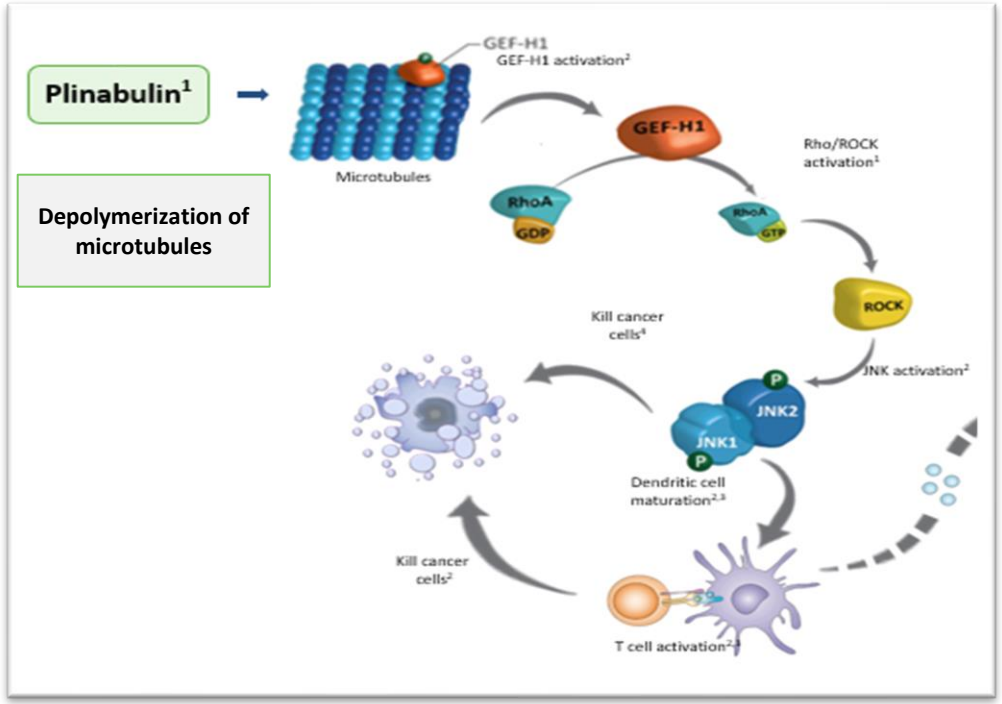
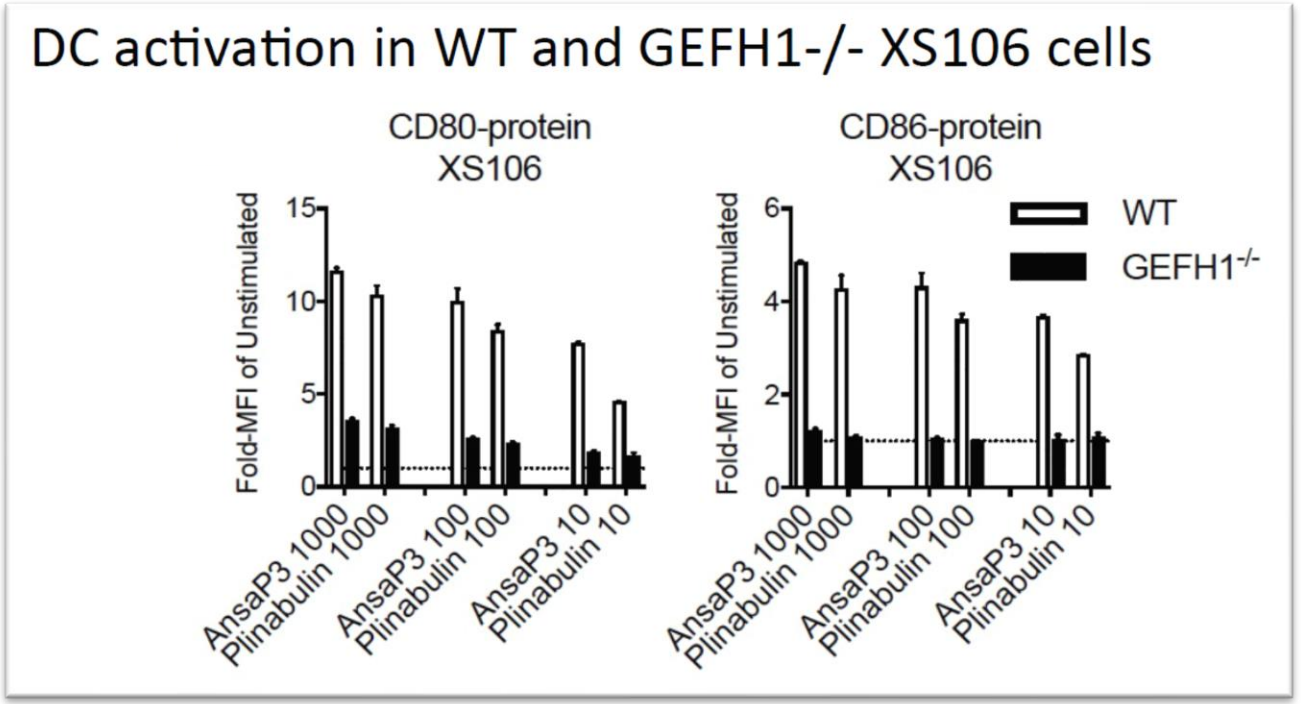
Plinabulin: Induces Innate and Adaptive Immunity via DC Maturation

By depolymerizing microtubules, plinabulin releases, or activates, immune defense protein GEF-H1.
This leads to dendritic cell maturation (the most potent APC).

Plinabulin Novel Target: Immune Defense Protein GEF-H1[1]



In WT DC cells, plinabulin can induce DC maturation, but not in GEF-H1 deleted DC cells[2]
CD80 and CD86 up-regulation are biomarkers for DC maturation



AnsaP3, Maytansinoid cytotoxic (positive control compound), too toxic for human study

[1] La Sala et al., Chem 5(11): 2969-2986 (2019)
[2] Kashyap et al., Cell Reports 28(13): 3367-3380 (2019)

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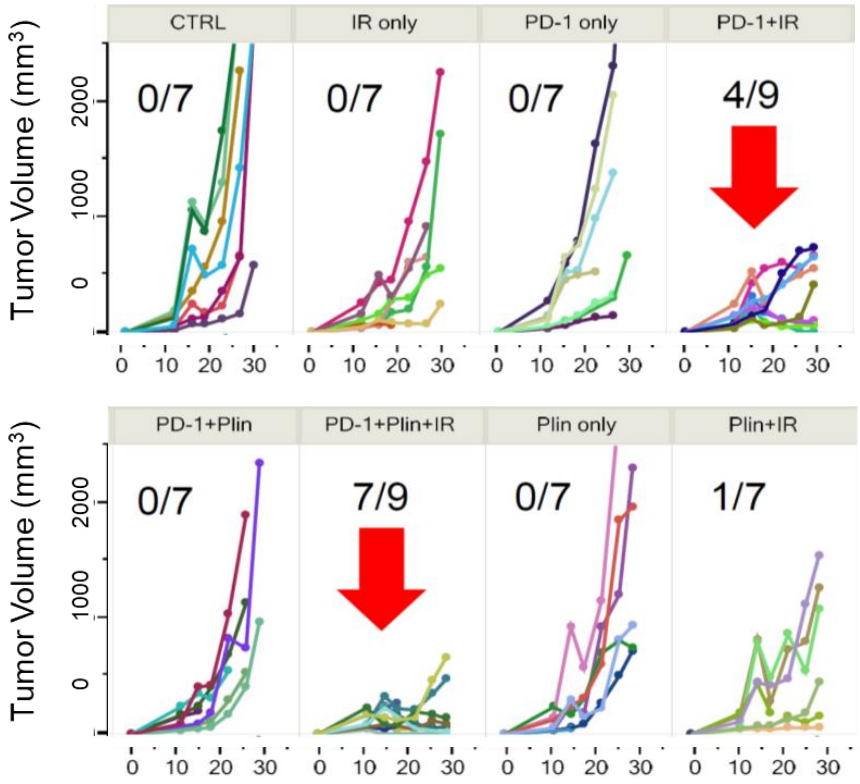
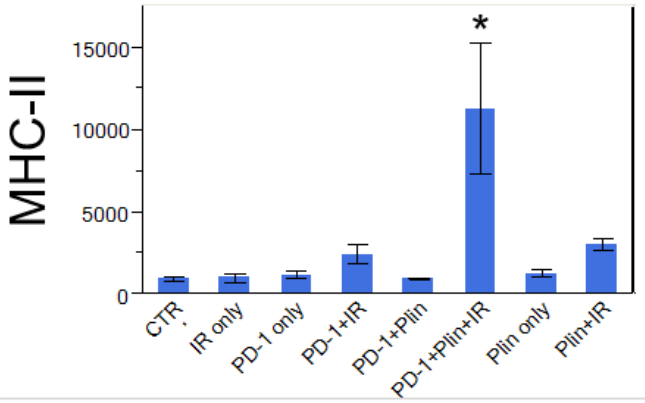
Radiation (RT)+anti-PD1+Plinabulin Triple Combination **POC in Animals** Provides Evidence of Plinabulin's Activity in **DC Maturation and T cell Activation**

Tumor reduction is most robust in triple I/O combination

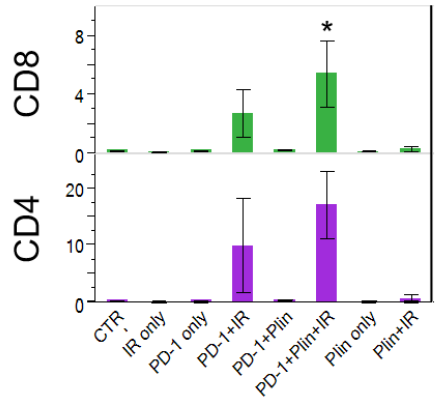


Plinabulin+RT+PD-1 induced ~80% tumor volume reduction in a preclinical cancer model

DC activation is most dramatic in triple I/O combination



T cell doubles in triple I/O combination vs. PD1 + IR



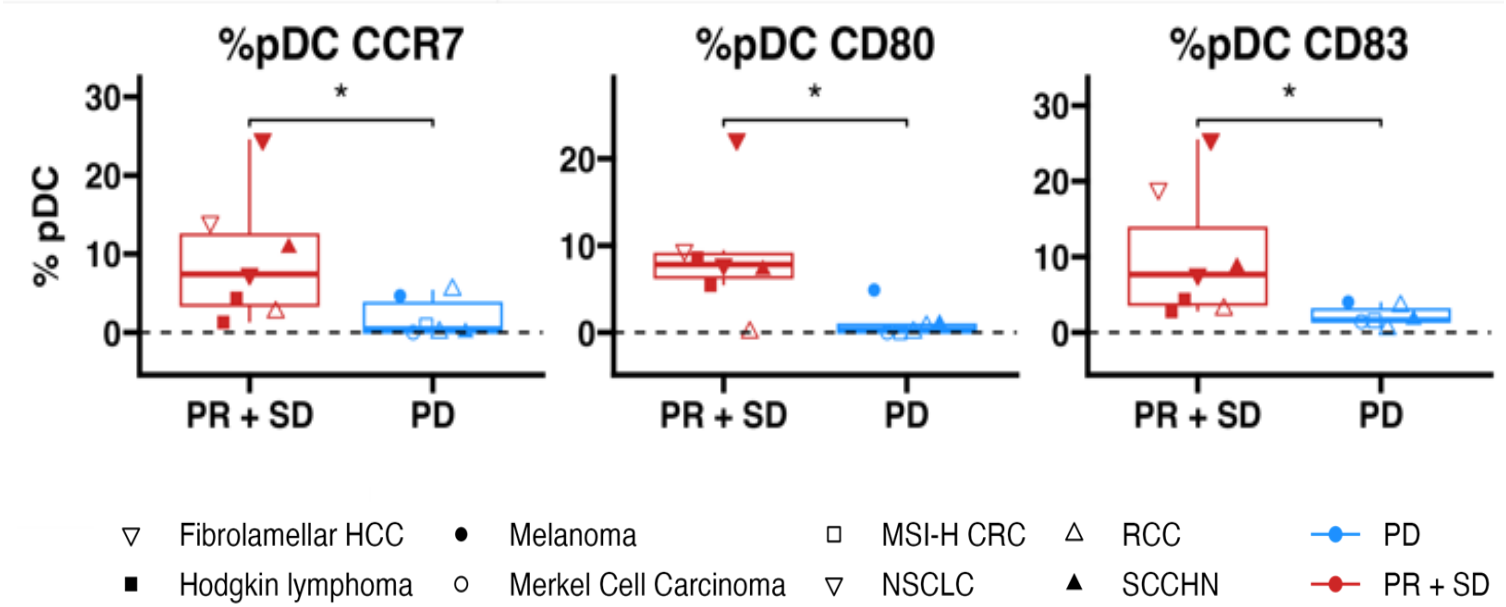
Plinabulin+ RT+PD-1

increased DC maturation and doubled CD4+ and CD8+ T cells in tumor 30 days after treatment

MOA PoC in Human: Plinabulin-Responding Patients Show Early Immune Activation Evidenced by Rapid DC Maturation in the Peripheral Blood

Phase 1b study in a number of IO Relapsed/Refractory solid tumors, DC maturation at cycle 1 Day 4 were observed in plinabulin-responding patients

Dendritic Cell Maturation & Migration



Eligibility:
Any cancer w/ progression on prior SOC anti-PD-1/PD-L1 agents;
Must have at least 1 site to be treated with radiation (RT) and biopsy, with another metastatic site to assess response.

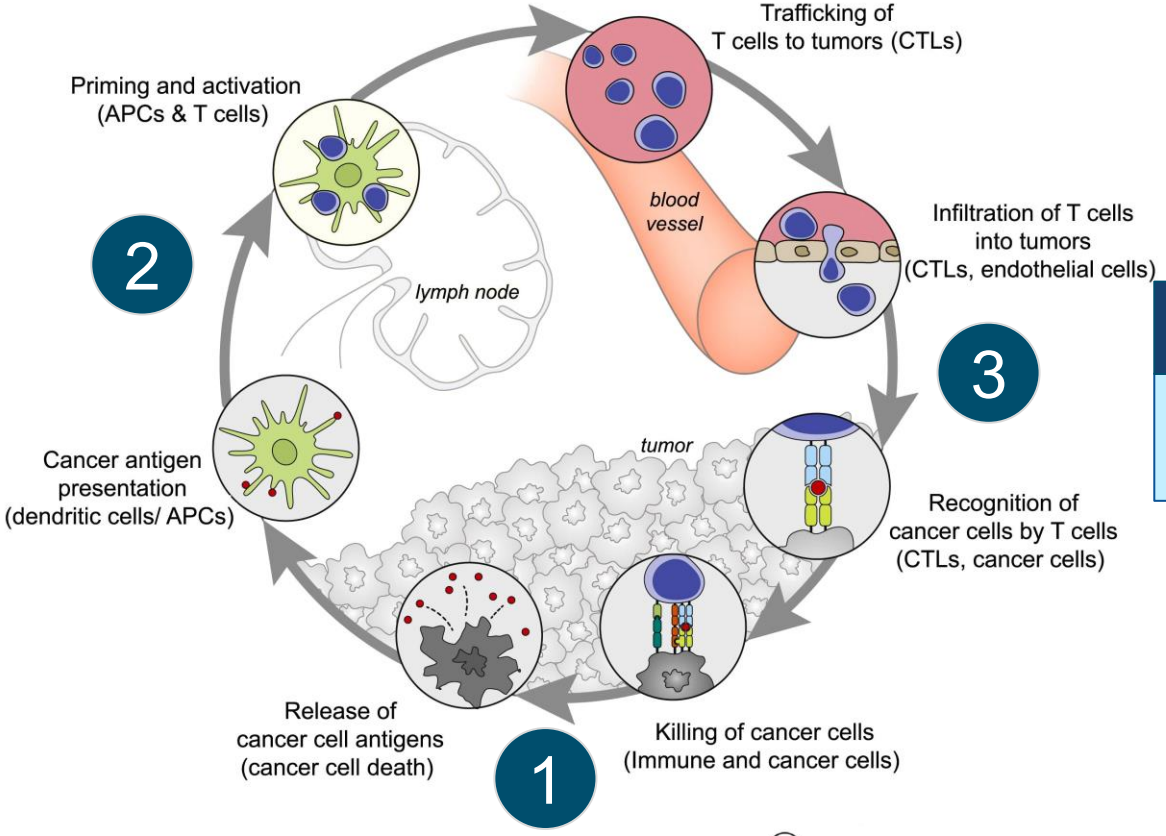
Regimen:
Cycle 1:
RT (day 1-3); Plinabulin (day 1, 3-6 hours after RT), anti-PD-1/PD-L1 (day 1).
Blood draw on Day 4.
Cycle 2 +:
Plinabulin (day 1, 3-6 hours after RT), anti-PD-1/PD-L1 (day 1).

Clinical Center: MD Anderson Collaboration (Publication under review)

Plinabulin Enhances the Cancer Immunity Cycle in Checkpoint Inhibitor-Resistant Patients (CINR)

② Plinabulin

Improved antigen presentation
Stimulate maturation of dendritic cells to increase antigen presentation;
DC sustains anti-tumor immunity[1]



③ Checkpoint Inhibitors

Anti-tumor T cell activation
Optimize T cell response

① Radiation/Chemotherapy

Release tumor antigens
For more potent anti-cancer effect

① Chemotherapy
Radiation Therapy
Oncolytic Viruses
Antibody Drug Conjugates
Targeted Therapy

1. Graph adapted from Mellman I, et al. Immunity 2023

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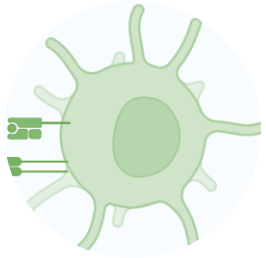
Plinabulin's Immunomodulation and Neutropenia-Mitigating Activities Position it as a Valuable Addition for Immuno-Chemotherapy Combination Regimens

These aspects result in an optimal scenario of added efficacy with potentially reduced toxicity.



Dendritic Cells

Plinabulin induces **dendritic cell maturation**

Enhanced antigen presentation and T cell priming

Tumor Vasculature

Plinabulin Targets **tumor vasculature**

Vascular Normalization

Enhances PD-1/PD-L1 targeting agents to boost T cell function, kill tumor cells, and Normalize vasculature

Improves safety*

Plinabulin **reduces chemotherapy-induced neutropenia**

Improved therapeutic index of chemotherapy-based regimens

Extends therapeutic duration and improves anti-cancer benefit

*To date, over 700 cancer patients have been treated with good tolerability.

Plinabulin Improves Overall Survival and Enhances Safety in 2L/3L NSCLC (Dublin-3 Study)

- Lancet Respiratory Medicine (publication on Sept 9, 2024)
- Oral Presentation at ISLAC 2024

2L/3L NSCLC (No Driver Mutation) Has Been a Historically Difficult Space in Which to Develop

Treatment options in 2L/3L NSCLC are limited

- Docetaxel-based therapies remains the standard of care in 2L/3L NSCLC (EGFR wild type). **No new therapy approved in the last 10 years.**
- However, **docetaxel-based therapies (SOC) demonstrate limited efficacy and are associated with >40% severe (grade 3/4) neutropenia.**
- Other approved agents:
  - **Ramucirumab + Docetaxel vs. Docetaxel**: OS HR=0.86, severe neutropenia 49% vs. 40%;[1]
  - **Pemetrexed vs. Docetaxel**: OS HR=0.99, severe neutropenia 5% vs. 40%.[2]
- Additionally, with immunotherapies moving to first line NSCLC, **there is a growing population of 2L/3L patients that are refractory to immunotherapy.**

2L, second line; 3L, third line; ADC, antibody drug conjugate; EGFR; epidermal growth factor receptor; HR, hazard ratio; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival, PD-(L)1, programmed death (ligand)-1; PFS, progression-free survival; SOC, standard of care; TKI, tyrosine kinase inhibitor; TTfields, tumor treating fields.

1. Garon et al. *Lancet*. 2014;384:665–673; 2. Hanna et al. *J Clin Oncol*. 2004;22:1589–1597.

Plinabulin Has Been Successfully Evaluated with Docetaxel in a Phase 3 Study with Advanced and Metastatic, Pre-treated NSCLC EGFR Wild Type Patients

Docetaxel + Plinabulin vs. Docetaxel + Placebo in Patients with EGFR Wild-Type NSCLC

Study Plan

- Global, randomized, single-blinded (patients only)
- Stratified by region (Asia/non-Asia), prior line (2L or 3L), ECOG (0-1/2), Prior PD-1/PD-L1 (yes/no)

Primary endpoint

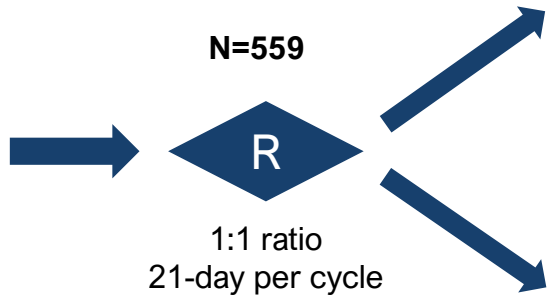
Overall survival (OS)

Secondary endpoints

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

Inclusion Criteria:

- Non-squamous or squamous NSCLC
- Stage IIIb/IV
- ECOG ≤ 2
- Progression during or after treatment with one or two treatment regimens containing a platinum
- Must have at least one measurable lung lesion
- **Prior checkpoint inhibitor therapy allowed**[1]



Plinabulin IV Infusion: 1 or 2 dose per cycle

DP:
Docetaxel
(75 mg/m2, day 1)
+ **Plinabulin**
(30 mg/m2, day 1, 8)

D:
Docetaxel
(75 mg/m2, day 1)
+ Placebo (day 1, 8)

[1] 85% CPI naïve; **15% failed PD-(L)1 blockade**

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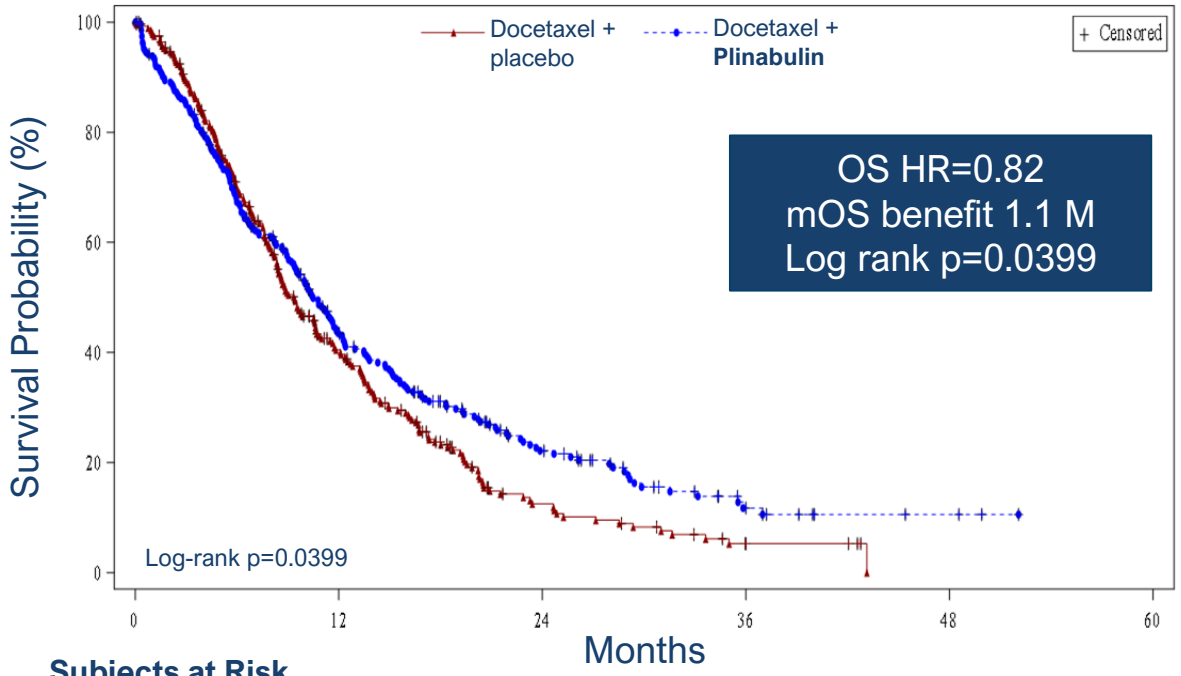
Balanced Baseline Characteristics

	Docetaxel + Placebo (n=281)	Docetaxel + Plinabulin (n=278)
Median age, y (range)	60 (25, 85)	61 (37, 82)
Sex, n (%)		
Male	207 (73.7)	199 (71.6)
Female	74 (26.3)	79 (28.4)
Tumor histology, n (%)		
Non-squamous	178 (63.3)	154 (55.4)
Squamous	100 (35.6)	120 (43.2)
Missing	3 (1.1)	4 (1.4)
ECOG, n (%)		
0	44 (15.7)	40 (14.4)
1	225 (80.1)	229 (82.4)
2 & missing	12 (4.3)	9 (3.2)
Regional distribution, n (%)		
Asian	245 (87.2)	243 (87.4)
Non-Asian	36 (12.8)	35 (12.6)
Cancer Stage, n (%)		
IIIB	41 (14.6)	50 (18.0)
IV	236 (84.0)	224 (80.6)
Prior PD-1/PD-L1 therapy received, n (%)		
Yes	57 (20.3)	49 (17.6)
No	224 (79.7)	229 (82.4)
Lines of prior therapy, n (%)		
First-line	212 (75.4)	204 (73.4)
Second-line	69 (24.6)	74 (26.6)

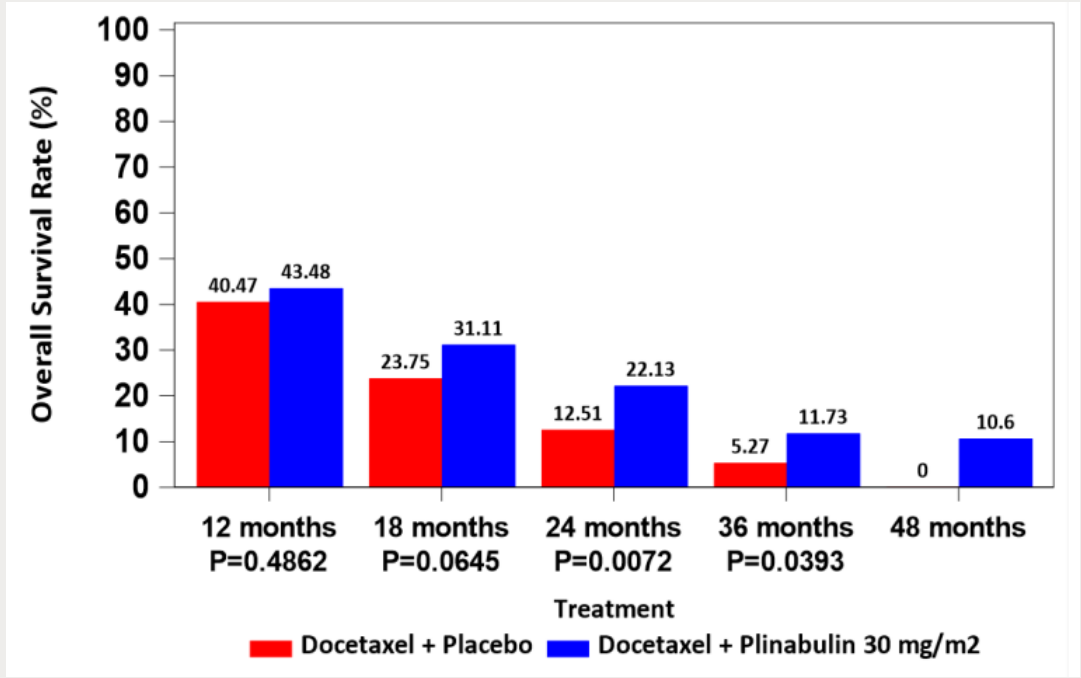
Plinabulin + Docetaxel Met its Primary Endpoint (OS) and Showed Significant Improvement in Long-term OS Rate



Subjects at Risk

Docetaxel (75mg/m2) + placebo					
281	97	21	4	0	0
Docetaxel (75mg/m2) + Plinabulin (30mg/m2)					
278	108	41	10	3	0

	Mean OS (SE)	Median OS (95% CI)	HR
Docetaxel	12.77 (0.676)	9.4 (8.4, 10.7)	
Plinabulin + Docetaxel	15.05 (0.848)	10.5 (9.3, 11.9)	0.82 (0.68, 0.99)

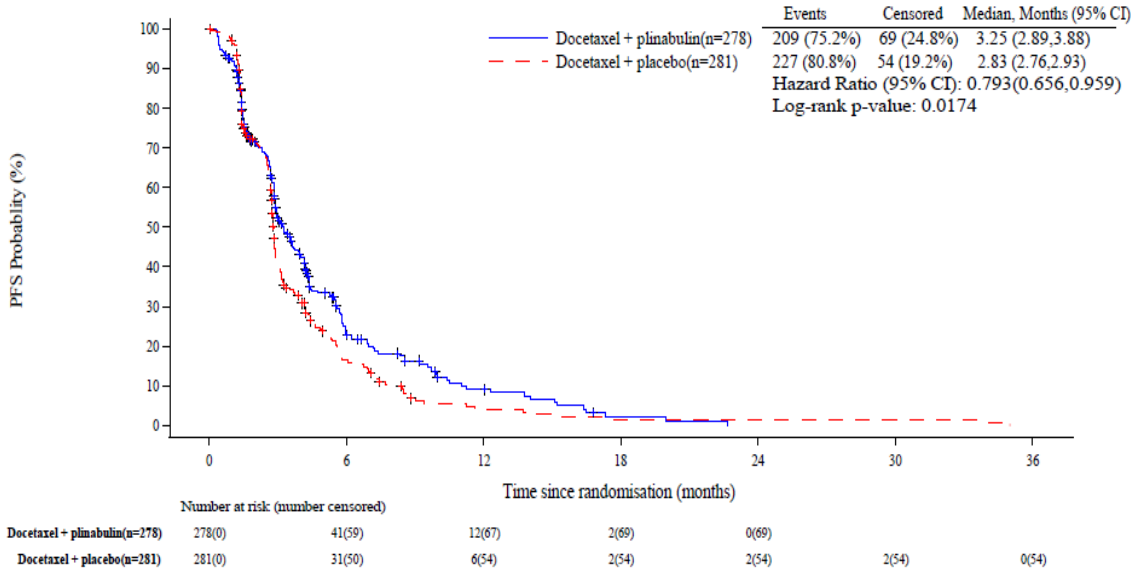


OS Rate Increase Results

- Significantly increased OS rate in 24 months, and 36 months (doubling benefit)
- 48m OS rate: D + Product X (10.6%) vs D (0%)

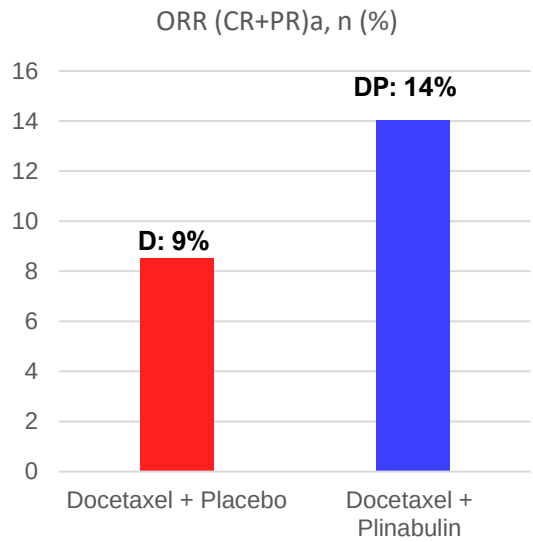
Plinabulin + Docetaxel Significantly Improved PFS and ORR

PFS



ITT	N	Median PFS Month (95% CI)	HR	Log rank P value
Docetaxel (D)	281	2.8 (2.76, 2.93)		
Plinabulin + Docetaxel (DP)	278	3.3 (2.89, 3.88)	0.79 (0.66, 0.96)	**p = 0.0174**

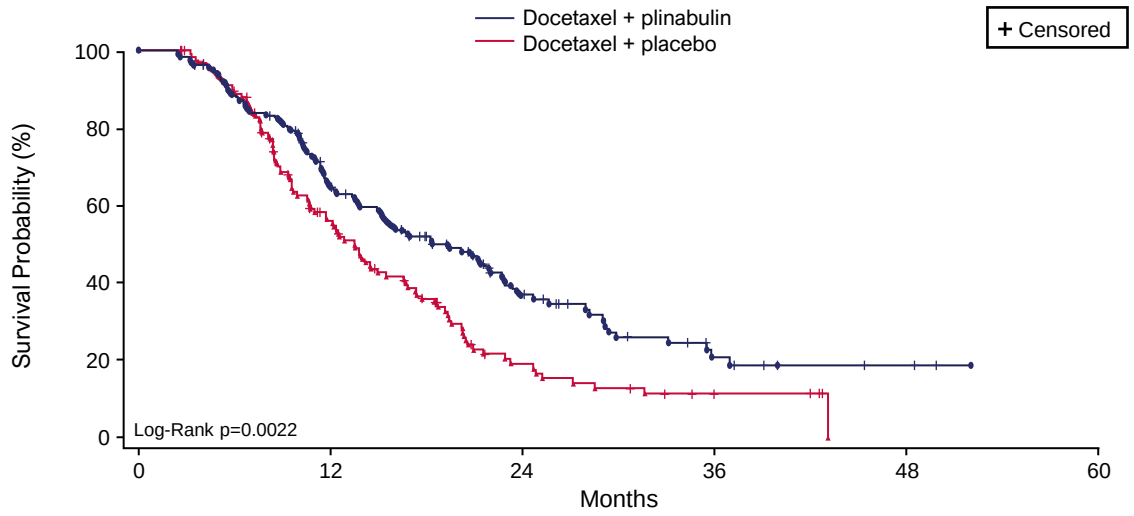
ORR



P value = 0.0404

Plinabulin Increases Cycles of Treatment and Improved OS Benefit with More Cycles of Treatment

OS K-M Graph for treatment cycles ≥4 cycles

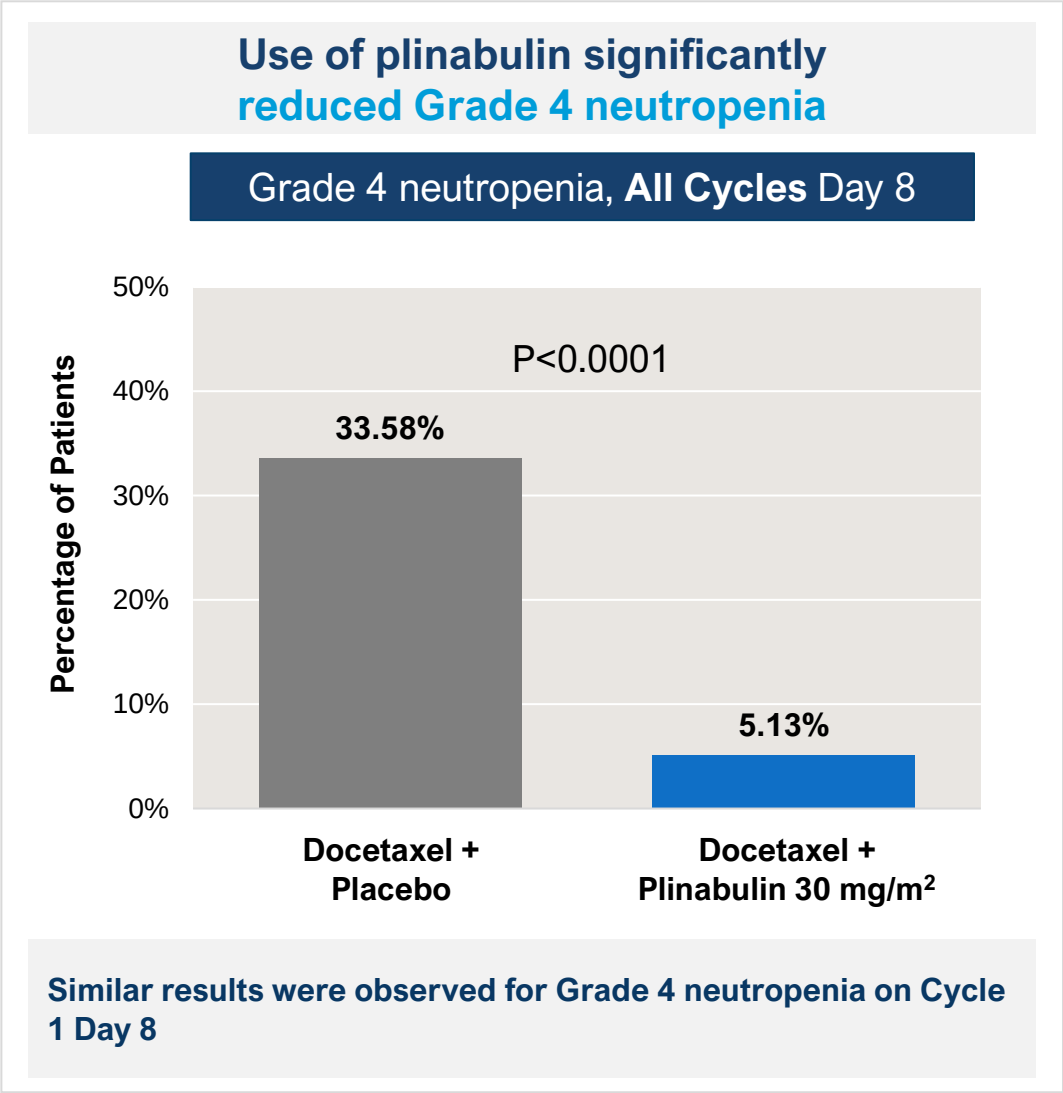


	N	Median OS	HR	P value
Docetaxel	128	13.5 (10.68, 16.54)		
Plinabulin + Docetaxel	133	18.3 (14.96, 22.88)	**0.634**	**P = 0.0022**

Consistently improved median OS observed with more treatment cycles

Number of cycles	Median OS in Months (95% CI)		p-value	HR (95% CI)
	Docetaxel + Plinabulin	Docetaxel + Placebo		
≥4 cycles	18·3 (14·96, 22·88) n=133	13·5 (10·98, 16·54) n=127	0·0027	0·639 (0·476, 0·858)
≥6 cycles	22·9 (19·40, 29·42) n=70	17·3 (12·36, 19·56) n=64	0·0021	0·507 (0·326, 0·788)
≥8 cycles	28·2 (21·99, NA) n=45	19·3 (13·77, 24·85) n=31	0·0121	0·453 (0·240, 0·854)
≥10 cycles	35·5 (22·72, NA) n=27	19·2 (12·39, 20·55) n=18	0·0001	0·174 (0·064, 0·473)
≥12 cycles	NA n=21	20·5 (12·39, NA) n=9	0·0142	0·155 (0·028, 0·855)

Plinabulin Significantly Reduce Grade 4 Neutropenia (>80% reduction) with less use of G-CSF

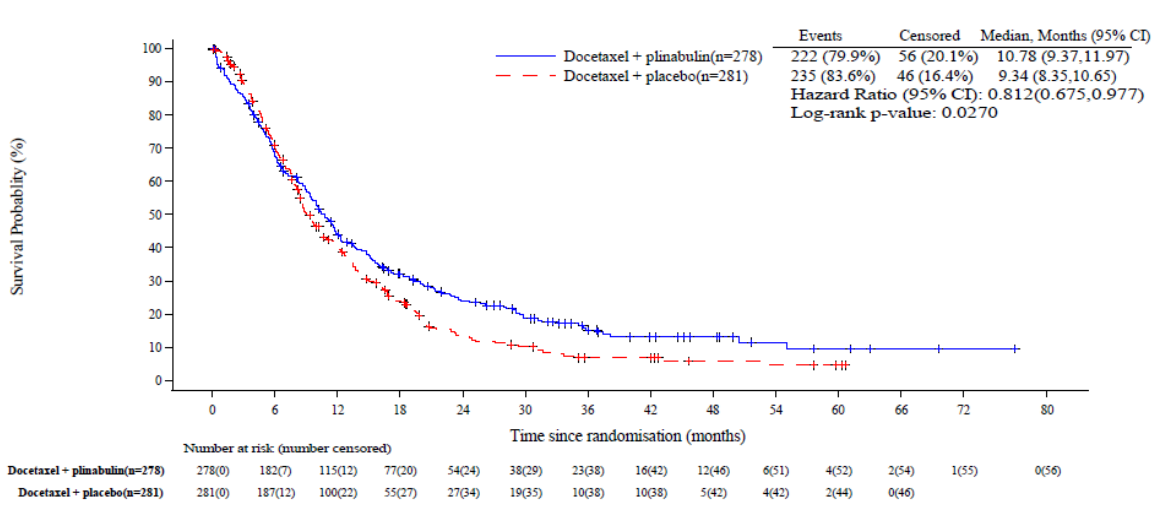


Less Use of G-CSF use in each treatment cycle for Plinabulin Arm

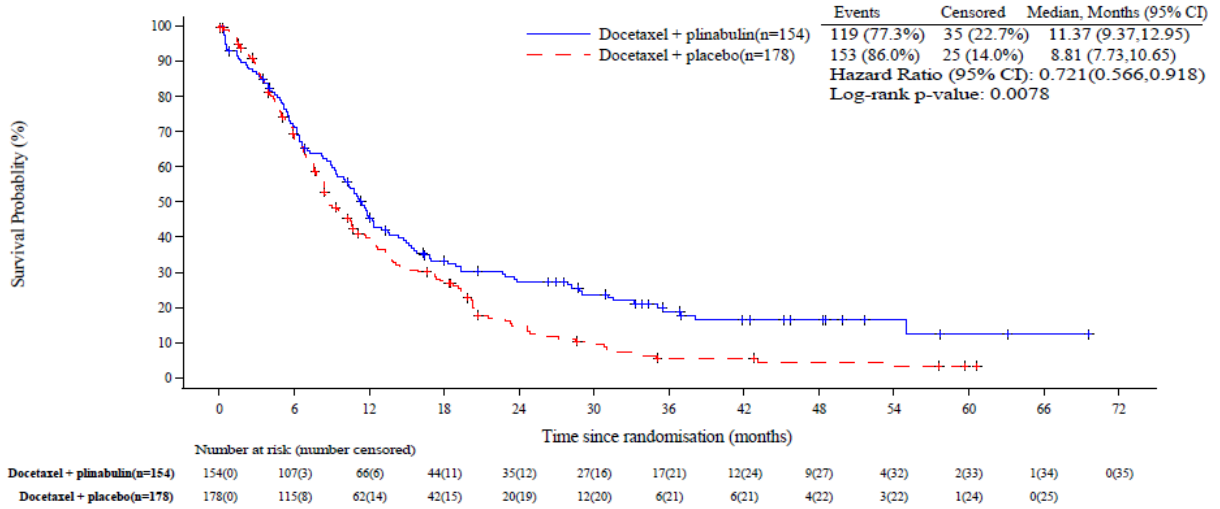
Treatment cycle	Docetaxel + plinabulin n/N (%)	Docetaxel + placebo n/N (%)
Any cycle	152/274 (55·5)	182/278 (65·5)
Cycle 1	111/274 (40·5)	141/278 (50·7)
Cycle 2	70/220 (31·8)	125/242 (51·7)
Cycle 3	47/160 (29·4)	71/155 (45·8)
Cycle 4	39/134 (29·1)	55/127 (43·3)

Consistent OS Benefit in 24-month follow up after Database Lock; Non-squamous OS HR=0.72

ITT



Non-squamous



ITT	N	Median OS (95% CI)	HR	Log rank P value
Docetaxel	281	9.3 (8.35, 10.65)		
Plinabulin + Docetaxel	278	10.8 (9.37, 11.97)	**0.81 (0.68, 0.98)**	**p = 0.0270**

Non-squamous	N	Median OS (95% CI)	HR	Log rank P value
Docetaxel	178	8.81 (7.73, 10.65)		
Plinabulin + Docetaxel	154	11.37 (9.37, 12.95)	**0.72 (0.57, 0.92)**	**P = 0.0078**

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DUBLIN-3: Treatment Related Adverse Events

	Docetaxel + Placebo N=278 n (%)			Docetaxel + Plinabulin N=274 n (%)		
TEAE	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any	276 (99.3)	85 (30.6)	119 (42.8)	273 (99.6)	141 (51.5)	52 (19.0)
Hematological						
Anemia	121 (43.5)	13 (4.7)	0	137 (50.0)	15 (5.5)	0
WBC decreased	189 (68.0)	102 (36.7)	33 (11.9)	160 (58.4)	47 (17.2)	32 (11.7)
Neutrophil count decreased	196 (70.5)	46 (16.5)	107 (38.5)	142 (51.8)	48 (17.5)	39 (14.2)
Platelet count decreased	48 (17.3)	2 (0.7)	1 (0.4)	77 (28.1)	12 (4.4)	6 (2.2)
Other TEAEs						
Diarrhea	62 (22.3)	3 (1.1)	0	118 (43.1)	23 (8.4)	1 (0.4)
Constipation	80 (28.8)	1 (0.4)	0	95 (34.7)	1 (0.4)	0
Nausea	67 (24.1)	0	0	100 (36.5)	3 (1.1)	0
Vomiting	39 (14.0)	1 (0.4)	0	82 (29.9)	6 (2.2)	0
Abdominal pain	23 (8.3)	1 (0.4)	0	42 (15.3)	0	0
Abdominal distension	13 (4.7)	0	0	29 (10.6)	2 (0.7)	0
Lung infection	42 (15.1)	23 (8.3)	1 (0.4)	31 (11.3)	15 (5.5)	2 (0.7)
Blood pressure increased	16 (5.8)	8 (2.9)	0	93 (33.9)	50 (18.2)	0
Hepatic enzyme increased	45 (16.2)	1 (0.4)	0	47 (17.2)	2 (0.7)	0
Weight decreased	24 (8.6)	0	0	32 (11.7)	1 (0.4)	0
Cough	77 (27.7)	2 (0.7)	0	64 (23.4)	1 (0.4)	0
Dyspnea	47 (16.9)	6 (2.2)	6 (2.2)	38 (13.9)	5 (1.8)	1 (0.4)
Hemoptysis	27 (9.7)	1 (0.4)	0	31 (11.3)	4 (1.5)	1 (0.4)

Plinabulin Successfully Improved Overall Survival Relative to SOC in 2L/3L NSCLC, an Achievement that has Eluded Other Novel Approaches

The addition of plinabulin as a single agent added to 2L/3L NSCLC (EGFR wt) standard-of-care docetaxel led to improved overall survival and enhanced safety

Efficacy

- Significant survival benefit in ITT (OS HR=0.82) and significant improvement in ORR and PFS
- Almost double 2-year and 3-year OS rate

Safety and tolerability

- The regimen is well tolerated. Side effects include transient hypertension which resolves in 4-6 hours, nausea, vomiting and GI side effects.
- Significant QoL benefit
- Docetaxel-induced grade 4 neutropenia was reduced (>80%), allowing increased treatment exposure

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A Phase 2 Study of Pembrolizumab (Pemb) plus Plinabulin (Plin) and Docetaxel (Doc) in Metastatic NSCLC Patients (pts) Who Failed First-Line Immune Checkpoint Inhibitor: Initial Efficacy and Safety Results

ESMO 2024, SITC 2024 presentation

Limited Options for 2L/3L NSCLC Patients Who Failed Prior PD-1/L1 Inhibitor

Historical Comparison Data

- **Docetaxel remains the standard of care** for patients with 2L/3L NSCLC without targetable alterations who progress on immune checkpoint inhibitors (ICI) with and without standard chemotherapy.

✓ Seven phase 3 studies, including ADC, PD-1 or PD-L1 combo with TKI had failed to show OS benefit vs. docetaxel.

- In the recent TROPION Lung-01 phase 3 study[1], a similar patient population had an overall response rate **(ORR) of 12.8%** and median progression free survival (**mPFS) of 3.7 months with docetaxel**. Overall survival is around 12 months.
- In NSCLC patients who progressed after clinical benefit from anti-PD-1/PD-L1 (PFS>=3 months), **Keytruda + docetaxel combination** had **mPFS of 5.5 months** and **ORR of 23.5%[2]**.

Mechanism of Acquired Resistance to Prior IO Therapies

- Acquired resistance in NSCLC or other solid tumors could be due to “T cell exhaustion” or “antigen presenting cell pathway mutation”[3].

BeyondSpring

1. Ahn et al., TROPION Lung-01 Study, Journal of Clinical Oncology, https://doi.org/10.1200/JCO-24-0154 (2024)
2. Salous T. et al., Cancer 129: 264-7 (2023); 3. Memon et al. Cancer Cell 42, 209–224 (2024)).

Merck IIT Phase II 303 Study: 2L/3L NSCLC, Progressed on PD-1/L1

Single Site (Peking Union Hospital) in China, Single Arm

N=47

- Metastatic NSCLC
- Progressed from PD-1/L1 monotherapy or in comb with platinum doublet
- 1L PFS > 6 months
- ECOG PS 0-1
- No prior use of docetaxel or plinabulin
- No need to use steroid to treat ILD, or pneumonia. EGFR, ALK, ROS1 target therapy not as primary therapy
- No brain metastasis, or no leptomeningeal metastasis

Regimen

- Keytruda 200mg D1 Q3W (up to 35 cycles)
- Plinabulin 30mg/m^2 D1 Q3W (Until PD, intolerable SAE, or withdraw from patient)
- Docetaxel 75mg/m^2 D1 Q3W Until PD, intolerable SAE, or withdraw from patient)

Endpoints

- Primary:
  - -ORR (RECIST 1.1)
- Secondary:
  - -PFS (RECIST 1.1)
  - -OS
  - -DOR (RECIST 1.1)
  - -OS rate
  - -Safety

Stage 1: Enroll 19 patients. Futility analysis: if not more than 2 patients with PR, stop the study. If > 2 patients with PR, process to stage 2.

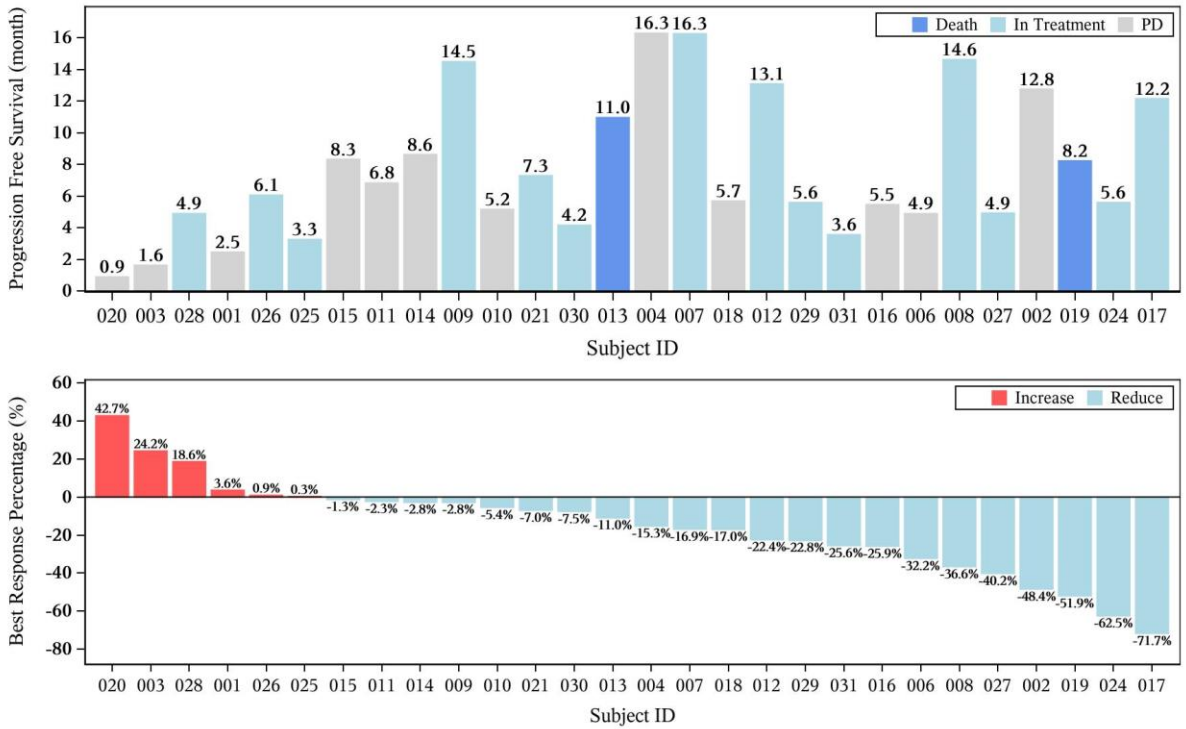
Stage 2: Total enrollment of 47 patients. If > 8 patients with PR, the study meets its objective.

Efficacy data (cut-off date on 29-Aug-2024) – 2024 SITC Presentation

Updated Analysis: 30 patients (ITT)
(Proportion of patients who had previously received Keytruda: 100%)
median follow-up time: 11.5 month (m)

Histology	
Squamous	43%
Non-squamous	57%
Primary endpoint	
Confirmed ORR (RECIST 1.1)	21.1%
Secondary endpoint	
mPFS (RECIST 1.1)	8.6 m
mDoR (RECIST 1.1)	11.4 m
DCR (PR+SD > 4 m)	89.3%*
mOS	NE

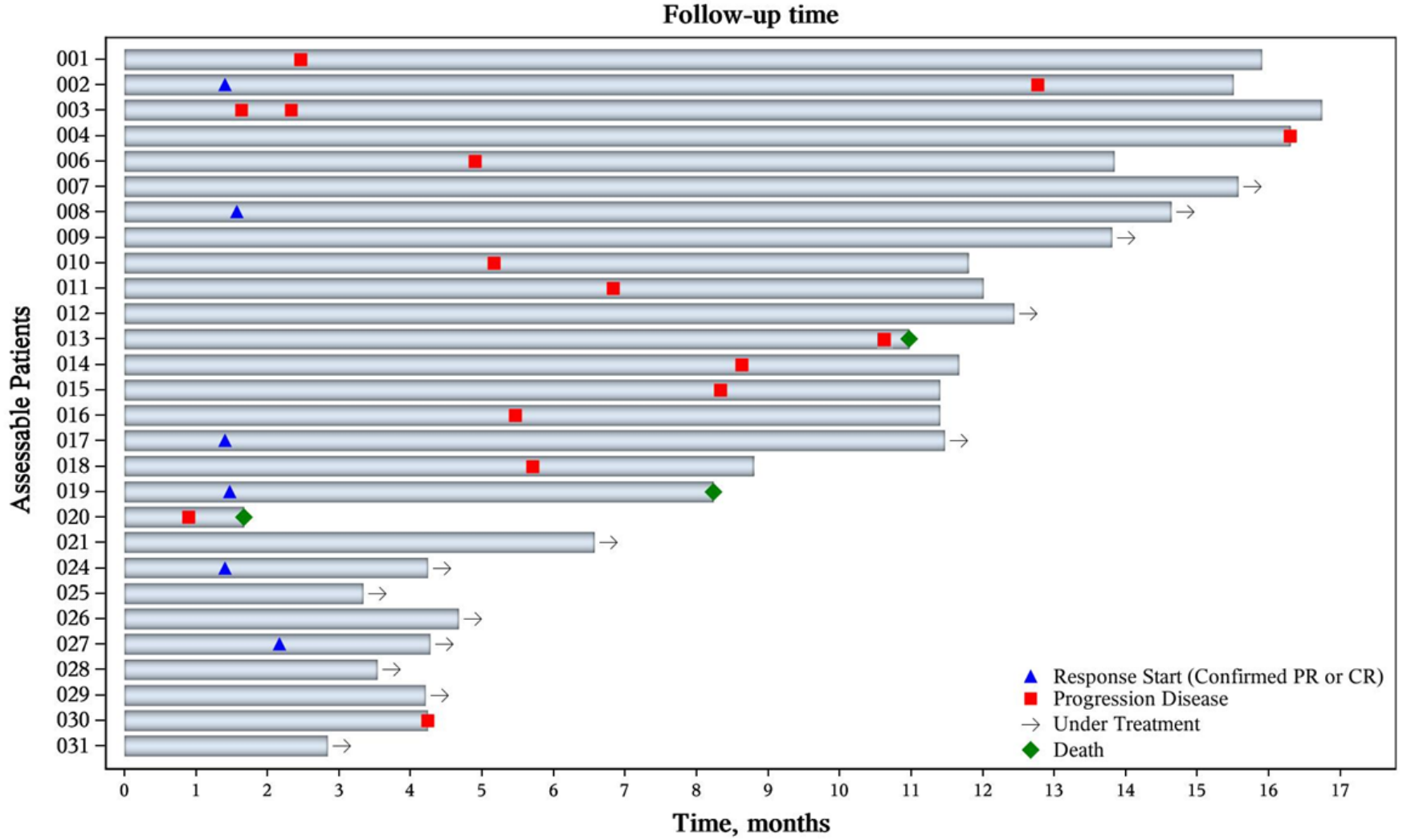
Best Change (%) in Target Lesions Sum of Diameters (SOD) and PFS



*25/28 – 2 withdrawn after first dose

Duration of Response

Swimmer Plot of Tumor Response (28 patients, Evaluable Population)



Safety Summary

Treatment-related adverse events (CTCAE 5.0 ≥ Grade 3)

System organ class, Preferred term	Pemb + Plin + Doc (N=30), n (%)
All TRAE, CTCAE ≥ Grade 3	14 (46.7)
Blood and lymphatic system disorders	5 (16.7)
Myelosuppression	4 (13.3)
Febrile neutropenia	1 (3.3)
Gastrointestinal disorders	4 (13.3)
Ileus	2 (6.7)
Diarrhea	1 (3.3)
Abdominal distension	1 (3.3)
Investigations	2 (6.7)
Neutrophil count decreased	2 (6.7)
Metabolism and nutrition disorders	1 (3.3)
Hyperglycaemia	1 (3.3)
Acidosis	1 (3.3)
Infections and infestations	2 (6.7)
Lung infection	1 (3.3)
Sepsis	1 (3.3)
Respiratory, thoracic and mediastinal disorders	1 (3.3)
Respiratory failure	1 (3.3)
Vascular disorders	2 (6.7)
Hypertension	2 (6.7)
Renal and urinary disorders	1 (3.3)
Acute kidney injury	1 (3.3)
Cardiac disorders	1 (3.3)
Atrial fibrillation	1 (3.3)

303 Study Summary

- Pemb plus Plin and Doc in patients with metastatic NSCLC who experienced disease progression after clinical benefit with ICI was associated with **double PFS and DCR** compared with historical controls of standard of care docetaxel (median PFS was ~3.7 months with docetaxel in the TROPION-Lung01 study)
- The combination is well tolerated.
- 303 study is ongoing and further analyses are underway.

Funding Source
Funding for this trial was provided by BeyondSpring and MSD China.

Encouraging RT+PD-1+Plinabulin Clinical Data Demonstrates Plinabulin's Dendritic Cell Maturation MOA in Responding Patients

Presentation at SITC 2023

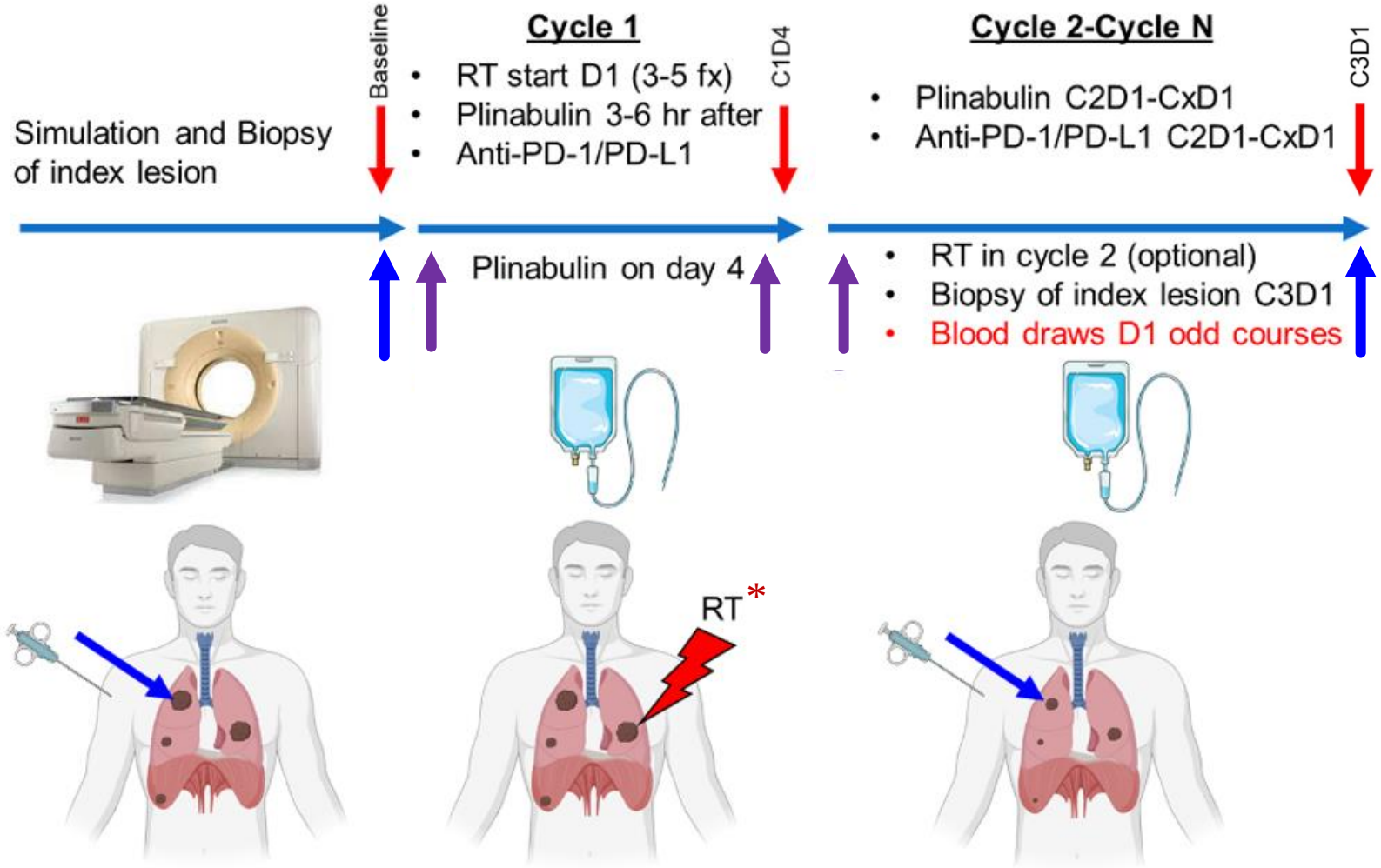
RT: Radiation therapy

2020-0296: Phase 1b Study to Evaluate Safety of Adding Plinabulin + RT/IO in IO Relapsed/Refractory Solid Tumors

Eligibility:
Any cancer w/ progression on prior SOC anti-PD-1/PD-L1 agents

Must have at least one site to be treated with RT and biopsy, with another metastatic site to assess response outside of index lesion

Study Design:
Open label, single-center
Phase Ib
3+3 design, DLT w/in 30 days

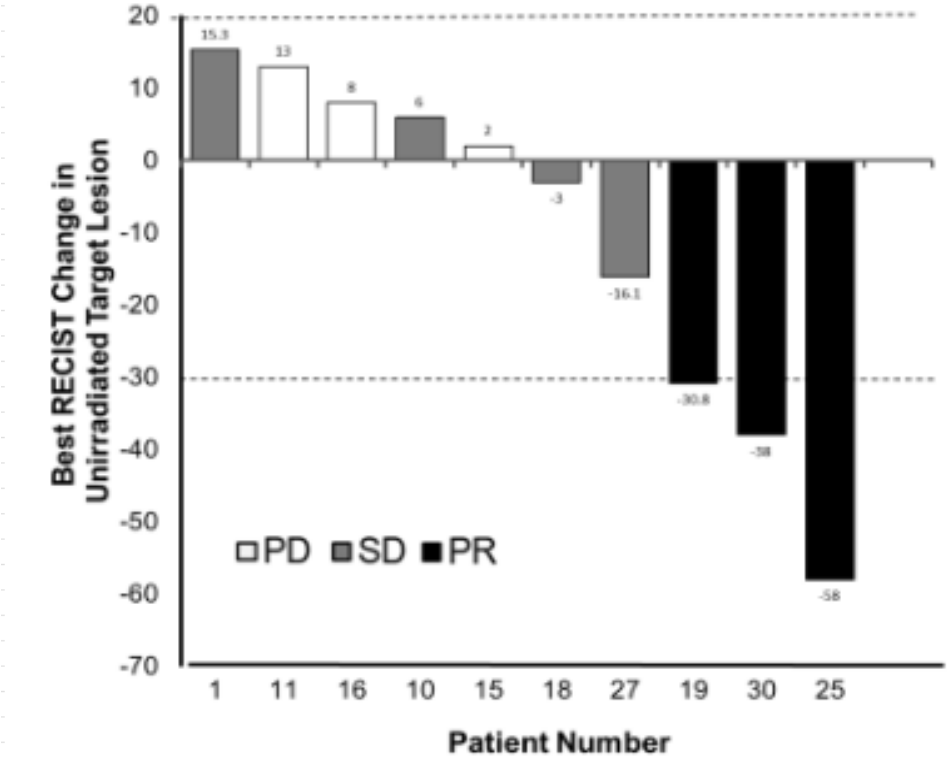


*** RT = 24 Gy/3 fx; 50 Gy/4 fx; 20 Gy/5 fx**

- **Primary endpoint: Safety and ORR/DCR**

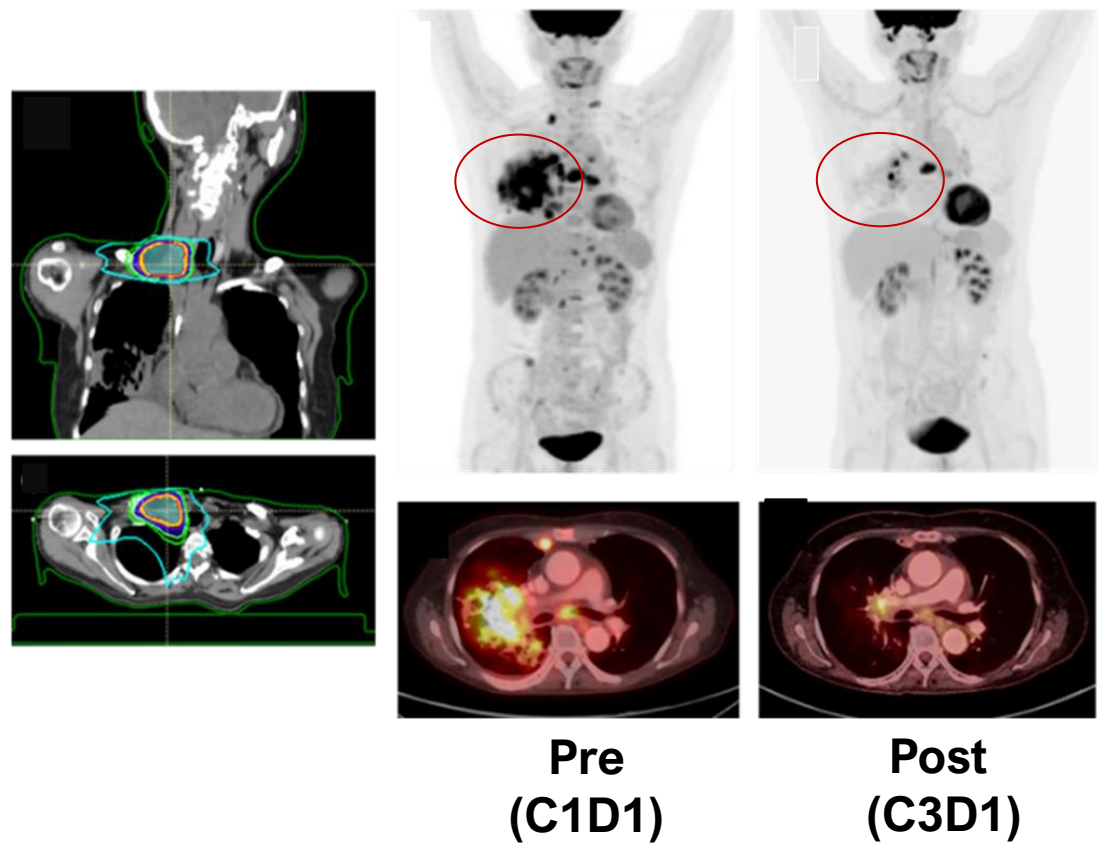
Clinical PoC in Efficacy: Plinabulin Triple Combo Produces Clinically Meaningful Responses in the Non-Irradiated Tumor Across Multiple Cancers in CINR

Topline Preliminary Data: presented at SITC 2023:
Plinabulin triple combination led to >50% DCR
(3 PR, 4 SD) in 10 IO-failed patients with Tumor assessment



Durable response has been observed in 2 Hodgkin lymphoma patients who progressed after 12 or 16 prior lines of therapy.

Systemic abscopal effect seen comparing baseline and C3D1 for one Hodgkin lymphoma patient (after 12 prior line failure)



Pre (C1D1) **Post (C3D1)**

Seven IO-relapsed/refractory cancers: NSCLC (Patient #1, #19); Merkel cell (#11); RCC (#16, #18); FL-HCC (#10); CRC (#15); HNSCC (#27); Hodgkin (#25, #30)

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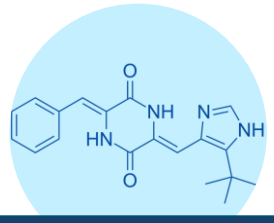
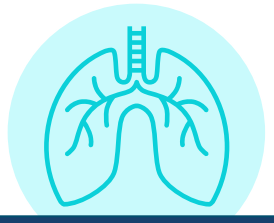
Plinabulin: Transforming Oncology with Novel Mechanisms for Patient Benefits





MOA in CINR	Clinical Success	Unmet Medical needs and Market Potential	Strong global patent protection
A first-in-class tubulin modulator that activates **dendritic cell** maturation and **tumor vasculature targeting** proliferation which **enables the cancer immunity cycle**	Successfully demonstrated significant **OS benefit** in 2L/3L NSCLC, as well as **reduction in severe neutropenia,** allowing **extended regimen duration**	Clinically enhanced the anti-tumor response to checkpoint inhibitors in combination with radiation or chemotherapy, even in **immunotherapy-resistant or progressed patient population**	BeyondSpring is a global company that has **Granted Patents to 2038 in 48 jurisdictions**

Plinabulin enhances the cancer immunity cycle with a minimal patient administration schedule

✓ **One intravenous infusion on day 1 of each cycle**

Strong rationale for Plinabulin combination with both immunotherapy agents and chemotherapy or ADCs, for potential improved anti-cancer benefit and reduced neutropenia in severe unmet medical needs

BeyondSpring

SEED Therapeutics: Target Protein Degradation (TPD 2.0) Company

TPD Targets 80% of Disease-Causing Proteins That are Currently Undruggable

Significant and Speedy Value Creation at SEED Therapeutics

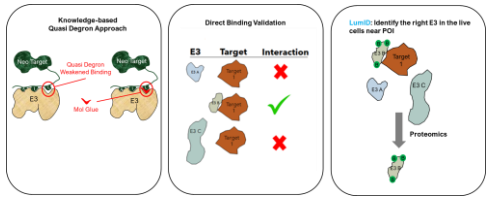
- SEED Uses Unique Target Protein Degradation (TPD) Technology for Novel Drug Discovery;
- TPD Platform Has the Potential to Address 80% of Disease-Causing Proteins That are Undruggable

Lilly Investment and R&D Collaboration

- $10 M Investment;
- $10 M upfront from R&D collaboration with Lilly, up to $780M milestone, tiered royalties
- BeyondSpring: $6 M Investment and TPD platform patents

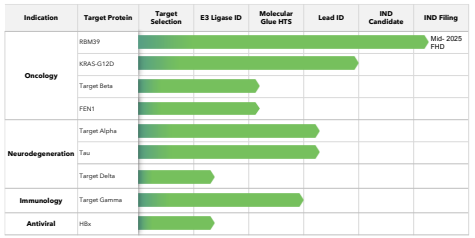
2020: SEED Founded

2021: Strengthened Proprietary Platform & Know-How



- Supported by multiple classes of patents
- Started R&D collaboration with Lilly

2023: Built R&D Infrastructure and Organization: Develop Diversified Pipeline



- 10,000 Sq. ft headquarters
- State of the art laboratories
- Expert in-house R&D team (>40 IND and >12 NDA track record)
- World-class leadership team and corporate board

2024: High Value Drug Candidates, Achieved Partnership Milestones and Financing

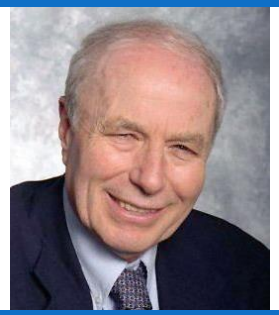
- **Achieved multiple Lilly collaboration milestones**
- Featured in 2 “Nature” Review articles in March and October 2024
- **Eisai Investment and R&D Collaboration**
  - Series A led by Eisai (first close of $24 M)
  - Concurrent R&D collaboration with Eisai with upfront and milestone payments up to $1.5B and tiered royalties

SEED Differentiation

Scalable Business Model	TPD has potential to target 80% of undruggable disease-causing proteins. > 600 E3 ligases to be used for multiple disease areas.
Target-Centric Differentiation	Identify the right E3 for POI to increase the success rate in drug discovery: Platforms using **Quasi-degron, LumID, and Basal Affinity**
Pioneering Effort	World-leading scientific founding team and experienced development team in successful translation of TPD platforms to 9 disclosed Assets
Two Prong Approach	De-risked revenue model: 1) R&D partnership for non-diluting financing (Lilly + Eisai); and 2) internal program development for value generation

World Class Leadership Team and Exceptional Insights in TPD Drug Development

Avram Hershko MD, PhD+



"**Godfather" of TPD**;
2004 Nobel Laureate;
Advisor to Millennium on developing **Velcade**

Ning Zheng, PhD+

Howard Hughes Professor, University of Washington; World's foremost **thought leader on E3 and MG**

Michele Pagano, MD +

Howard Hughes Professor, NYU Medical School;
Global **thought leader on TPD biology and application**

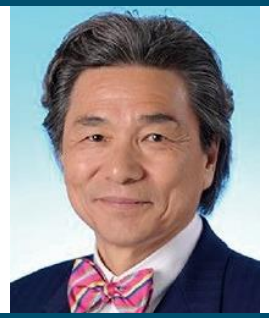
Lan Huang, PhD + *
(Chairman & CEO)

E3 structural expert; Serial biotech entrepreneur with **20+ years** of drug development experience, including assets that are NDA-ready

James Tonra, PhD*
(President & CSO)

20+ years of drug discovery experience that led to **5 NDAs**; Ex leadership role in Regeneron, Millennium, ImClone, Kadmon, and BYSI

Ko-Yung Tung, JD*

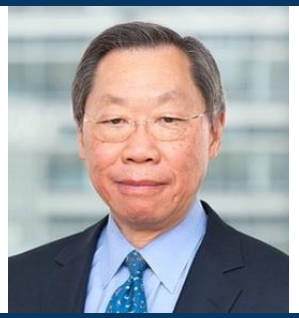


Former Eisai director, World Bank general counsel, and lecturer at Harvard and Yale Law School; Expert in law and international business

Linus Lin, PhD*

Global head of Lilly Chorus; Ex GM of Lilly China R&D Center, Head of Chemistry at WuXi AppTec, and led multiple drug discovery teams at Merck

Jackson Tai*



Wuxi Biologics Audit Committee Chair; retired board member for Lilly, HSBC, Mastercard; former DBS Bank CEO, former J.P. Morgan & Co, investment banker

Yoshiharu Mizui, PhD*

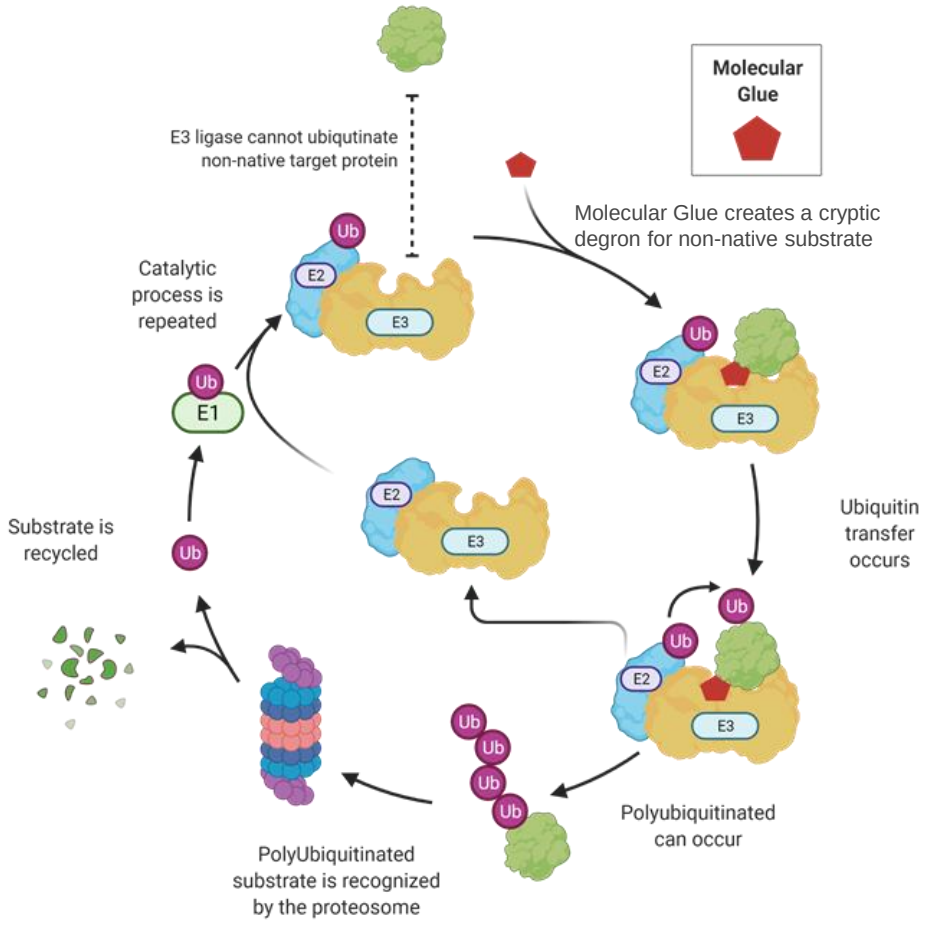
Founder and President of Eisai Innovations, Inc.;
former Global Business Development and Strategy Head in Eisai's Oncology Business Group

BeyondSpring

+SEED Co-founder and Scientific Advisory Board Member
*Board Member

TPD Development History and Recent Renaissance

TPD Process



SEED Co-Founders played pivotal roles in the advancement of TPD field

- 1996: **Dr. Michele Pagano** discovered cell cycle regulation by TPD, including E3 ligases; published in *Science*
- 1999: **Dr. Lan Huang** solved the 1st of two E3 structures (HECT domain E3); published in *Science*
- 2002: **Dr. Ning Zheng** solved the 2nd of two E3 structure (Ring-finger E3); published in *Nature*
- 2003: US FDA approved **Velcade**, the first proteasome inhibitor for multiple myeloma. **Dr. Avram Hershko** advised on Velcade development. Other companies started to develop new E3 inhibitors with no success
- 2004: **Dr. Avram Hershko won Nobel Prize** for his pioneering work in discovering all essential enzymes for TPD, including E1, E2, E3, and dproteasome
- 2007: **Dr. Ning Zheng coined the term "Molecular Glue (MG)"** after solving TIR1 E3 structure and discovering the true function of Auxin, a plant hormone and the **first natural MG to be identified**; published in *Nature*
- 2010-2014: Revolutionary discovery of the mechanism of action of **Revlimid** (for treating multiple myeloma, had peak global annual sale of $12.8b), a derivative of thalidomide, is in fact a MG, that binds to Cereblon (a E3) to degrade Ikaros (a mutated POI). This discovery, published in *Nature,* ushered in the **renaissance of TPD drug discovery**
- 2020: **SEED** was founded to develop "molecular glues" for undruggable targets.

Controlled Protein Degradation: Reprogramming Ubiquitin Ligases with Molecular Glues to Target Un-ligandable Proteins

LIMITATIONS:

× Bi-functional molecule
× >500 Da (may limit cell availability)
× High affinity on both ends (ligandable pockets required)
× Mostly limited to two UBLs

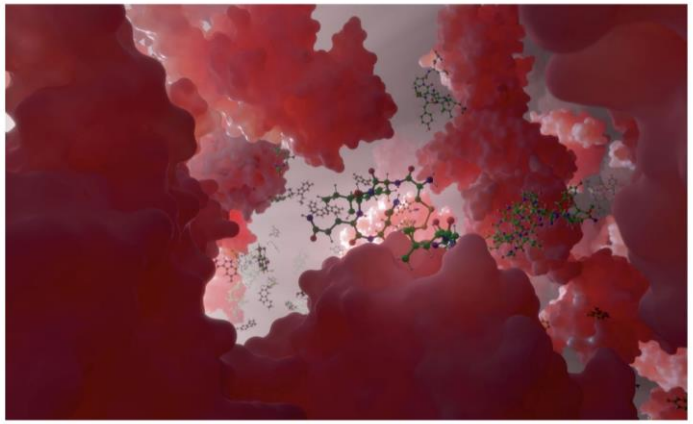
ADVANTAGES:

✓ Involves a single non-chimeric small molecule
✓ Small enough to be drug-like compounds
✓ Does not need high affinity on either sides (ligandable pockets not required)
✓ Many UBLs can be used (Substrate-centric)

“Nature Biotechnology” Review on “The Glue Degraders” (3/6/2024)

News feature

https://doi.org/10.1038/s41587-024-02164-9



THE GLUE DEGRADERS

Companies are hoping to discover small molecules that remove undruggable proteins. It won't be easy. **By Ken Garber**

In December 2023, two days after the US Food and Drug Administration approved separate gene editing and gene therapy treatments for sickle cell disease, Novartis biochemist Pamela Ting made a plenary presentation at the American Society of Hematology annual meeting[1]. She described a phenotypic screen that yielded hits causing a surge of fetal hemoglobin, the same protein that the recently approved gene editing therapy is engineered to produce. But unlike that treatment, which is priced at $2.2 million, Novartis's compounds are small-molecule protein degraders, molecular 'glues' that would be much cheaper to produce and administer. Animal studies were positive. "We are currently conducting the experiments necessary to translate these findings to a human clinical trial," Ting said at the meeting. The Novartis work is the latest sign that molecular glue degraders, which hijack the cell's disposal machinery to remove disease-related proteins, have arrived.

Much of pharma is invested, directly or through partnerships. In 2019 Bristol Myers Squibb spent $74 billion to acquire Celgene and its portfolio of molecular glue degraders. More than two dozen biotech companies are now seeking these drugs (Table 1). "We're very active in this space and see tremendous potential in molecular glues," says Ryan Potts, head of the induced proximity platform at Amgen.

Yet the field faces some serious obstacles. Prospective screening for molecular glue degraders is a major undertaking (Fig. 1). It's often done in cells, unlike standard biochemical assays with recombinant proteins, adding time and expense, and involves extensive follow-up work to validate hits and understand mechanism of action. And those hits are rare because it is hard to drug protein–protein interactions. With hit rates low, small-molecule libraries must be sizable. And the field does not yet know what chemical features molecular glues have in common, making it difficult to select these libraries. Biological information on the more than 600 E3 ligases – the enzymes that molecular glues recruit to degrade a drug's target – is scant, except for a handful of these proteins. For all these reasons, molecular glue discovery remains a high-risk enterprise. "The field needs a success story," says Simon Bailey, head of drug discovery at Plexium.

nature biotechnology

Garber, *Nature Biotechnology* (2024)

SEED was prominently featured in “Nature Biotechnology” Review.

Table 1 | Selected molecular glue degrader companies discussed

Company	Pharma partners	Discovery approach	Deployed E3 ligases	Lead program
Monte Rosa Therapeutics	Roche	Remodel cereblon to recruit neosubstrates; proximity assays, proteomics	Cereblon	MRT-2359, GSPT1 degrader, phase 1 (cancer)
Plexium	Amgen, AbbVie	Miniaturized, cell-based DNA-encoded library screening; target-centric	Cereblon, DCAF11, others undisclosed	IKZF2 degrader, phase 1 (cancer) December 2023
Seed Therapeutics	Eli Lilly	Target centric; detect basal E3–target interactions; proximity assays	Working with 25–30 E3s, including DCAF15	ST-00937, RBM39 degrader (cancer), IND filing, 2H24
Novartis	Dunad Therapeutics	Phenotypic screens, cereblon binders, others undisclosed	Cereblon, others undisclosed	Wiz degrader (sickle cell anemia), IND-enabling studies
Proxygen	Boehringer Ingelheim, Merck KGaA, Merck & Co.	Broad range, from unbiased phenotypic screens to target-centric	Many; undisclosed	Undisclosed
A-Alpha Bio	Amgen, Bristol Myers Squibb, Kymera Therapeutics	Detect basal E3–target interactions using yeast cell surface display, mutagenesis to interrogate interface	Many; undisclosed	Undisclosed

Others in this space include Ambagon Therapeutics, Astellas Pharma, AstraZeneca, Bayer, Biotheryx, Celgene (Bristol Myers Squibb), ChemPartner, Coho Therapeutics, Degron Therapeutics, Gandeeva Therapeutics, GSK, GluBio Therapeutics, Magnet Biomedicine, Neomorph, Orionis Biosciences, PhoreMost, Pin Therapeutics, Progenra, Proximity Therapeutics, Ranok Therapeutics, Revolution Medicines, Salarius Pharmaceuticals, SK Biopharmaceuticals, SyntheX and Triana Biomedicines. IND, Investigational New Drug.

Sticking without glue

Molecular glue company Seed Therapeutics, like Proxygen, is looking beyond cereblon. It's a majority-owned subsidiary of Beyond-Spring Pharmaceuticals, a drug company co-founded by Lan Huang, who published the first E3–E2 crystal structure[15], and Ning Zheng, who solved the structure of auxin bound to its transport inhibitor response 1 (TIR1) receptor[4].

Seed emphasizes proper E3 selection. The discovery process is lengthy: pick a candidate E3 on the basis of complementarity with the target protein (as predicted by AlphaFold and other computational methods) and cell location of the E3; detect a basal E3–target interaction in a cell system; confirm ability of the E3 to ubiquitinate the target; and perform high-throughput screening for degraders, followed by validation assays and then medicinal

“Nature Reviews Drug Discovery” Review on “Protein Degraders Push into Novel Target Space” (10/14/2024)

News & analysis

News https://doi.org/10.1038/d41573-024-00170-9

Protein degraders push into novel target space

By Asher Mullard

Clinic-ready molecular glues and heterobifunctional PROTAC drugs are taking targeted protein degradation into uncharted territory.

With the rise of targeted protein degraders over the past decade, early adopters promised that these small molecules would be able to unlock previously intractable targets. A first wave of molecular glue and heterobifunctional degraders mostly focused on well-validated targets. A second surge is now pushing into more novel target space.

“We’re on the cusp of a revolution,” says Neil Bence, head of oncology discovery at Bristol Myers Squibb (BMS), which is using both molecular glues and ligand-directed degraders to breakdown novel targets in cancer and other indications.

Traditionally hard-to-drug targets – including transcription factors, GTPases and guanine nucleoside exchange factor (GEFs) – are increasingly within reach, shows the growing degrader pipeline (Table 1).

“We’re on the cusp of a revolution”

This is enabling molecular glue degraders – small molecules that reshape an E3 ligase to make it tag targets with ubiquitin, shunting problem proteins to the cell’s proteasomal recycling system – to expand beyond their oncology origins. BMS is testing a transcription-factor-degrading glue for sickle cell disease, while Monte Rosa has advanced its VAV1-targeted GEF degrader into the clinic for autoimmune diseases.

Heterobifunctional degraders – larger dumbbell-like molecules that bind a target of interest with one end and an E3 ligase with the other – are making headway in novel target space too. Kymera is advancing a first-in-class degrader against the immune-mediating transcription factor STAT6, for example, while both BMS and Arvinas are taking on the oncogenic transcription factor BCL6.

Zoran Rankovic, director of the Centre for Protein Degradation at the Institute of Cancer Research, is buoyed by this progress. Degraders against previously drugged targets could be a boon to patients, he explains, if they can outperform approved inhibitors. But most of the human proteome is still undrugged, and the bigger opportunity for degraders is to push these boundaries.

The field has a way to go, he adds. Glue degrader discovery remains limited as yet mostly to serendipitously identified targets, and heterobifunctional degraders remain constrained by ligandability issues and rational-design limitations. But researchers are making progress across the entirety of the degrader modality.

“This is a hype that actually lives up to its promise,” says Rankovic.

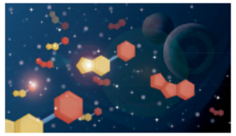
“This is a hype that actually lives up to its promise”

Old glues, new clues

Interest in targeted protein degraders has exploded in the past 10 years, and dozens of companies are now operating in this space. While heterobifunctional drug discovery companies were faster out of the gate, the ranks of the glue degrader biotechs are growing too – fuelled especially by the field’s understanding of how the FDA-approved myeloma drug lenalidomide and related immunomodulatory drugs (IMIDs) bind and reshape the E3 ligase cereblon to ubiquitinate the transcription factors IKZF1 and IKZF3. Other small-molecule glues might be able to reshape cereblon to take on other targets too, researchers quickly realized.

The first programmes to advance into the clinic, however, took on targets that were also degraded by lenalidomide. Celgene, now part of BMS, for example, worked quickly with its lenalidomide analogues to discover and optimize CC-92480, now mezigdomide, to breakdown IKZF1 and IKZF3. That drug is now in phase III development for myeloma. The kinase CK1α was another low-hanging fruit that is degraded by lenalidomide.

A further stepping stone was GSPT1, a GTPase that researchers pulled down during an immunoprecipitation assay of cereblon and a lenalidomide analogue. GSPT1 helps the protein-making machinery to disengage



from completed proteins, and its blockade kills cells – especially fast-growing cancerous ones – creating oncology applications for the previously undrugged GTPase target. BMS first advanced its GSPT1 degrader CC-90009 into the clinic in 2016, but has since terminated that glue for undisclosed reasons.

“GSPT1 degradation shuts down global protein translation, and there are a number of adverse events that are likely to be associated with that,” cautions Ian Churcher, a consultant with Janus Drug Discovery and a former degrader developer at both Amphista and GSK. “It’s all about therapeutic index.”

At BMS, that now means using an antibody–glue conjugate to better deliver the degrader to cancer cells. Its BMS-986497, acquired from Orum Therapeutics, consists of a GSPT1-degrading glue tacked on to a CD33-targeted antibody, to home in on malignant B cells.

“To improve both the efficacy and tolerability of GSPT1 degradation, an antibody–conjugate approach would be ideal,” says Bence. “We’re excited to see how this type of approach performs. It’s a really exciting time right now for degrader–antibody conjugates.”

BMS has also moved a glue degrader forward against another transcription factor for sickle cell disease, but as yet has not disclosed its target. “Stay tuned,” says Bence.

A cereblon-based glue degrader that targets the transcription factor WIZ can boost fetal haemoglobin levels in mice and primates, Novartis reported this year, showcasing one way a glue could be useful in sickle cell disease.

Target hopping

Monte Rosa was another early mover against GSPT1, developing MRT-2359. Clinical data as yet shows that this glue has a viable therapeutic index and a tolerable safety profile in patients with MYC-driven solid tumours.

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SEED was prominently featured in “Nature Reviews Drug Discovery”.

Table 1 | Degraders move into novel target space

Target	Target properties	Molecule (degrader type)	Company	Indication	Status
Newly prosecuted targets					
GSPT1	GTPase, translation termination factor	BMS-986497 (antibody–glue conjugate); MRT-2359 (glue); CC-90009 (glue)	BMS/Orum; Monte Rosa; BMS	Haematological malignancies; MYC-driven cancer	Phase I; Phase I/II; Discontinued
VAV1	GEF, scaffold protein	MRT-6160 (glue)	Monte Rosa	Autoimmunity	Phase I
Not disclosed	Transcription factor	HbF-activating CELMoD (glue)	BMS	Sickle cell disease	Phase I
WIZ	Transcription factor	NA (glue)	Novartis	Sickle cell disease	Preclinical
BCL6	Transcription factor	ARV-393 (heterobifunctional); BMS-986458 (heterobifunctional)	Arvinas; BMS	B-cell malignancies	Phase I; Phase I
STAT6	Transcription factor	KT-621 (heterobifunctional)	Kymera	Allergic diseases	Phase I in 2024
IKZF2	Transcription factor	Helios CELMoD (glue); PLX-4545; DKY709 (glue)	BMS; Plexium; Novartis	Cancer	Phase I; Phase I; Discontinued
HuR (ELAVL1)	mRNA stability regulator, RBP	NA (glue)	Degron	Cancer	Preclinical
Previously prosecuted targets, without approvals					
IRAK4	Kinase, scaffold protein	KT-474 (heterobifunctional)	Kymera/Sanofi	AD and HS	Phase II
LRRK2	Kinase, scaffold protein	ARV-102 (heterobifunctional)	Arvinas	Parkinson’s disease	Phase I
STAT3	Transcription factor	KT-333 (heterobifunctional)	Kymera	Cancer	Phase I
MDM2	E3 ligase	KT-253 (heterobifunctional)	Kymera	Cancer	Phase I
RBM39	Splicing factor, RBP	NA (glue)	Seed	Cancer	Phase I in 2025
NEK7	Kinase	MRT-8102 (glue); NA (glue)	Monte Rosa; Novartis	Inflammation	Preclinical; Preclinical

Pipeline data from Cortellis database and company websites. AD, atopic dermatitis; CELMoD, cereblon E3 ligase modulatory drug; GEF, guanine nucleotide exchange factors; HS, hidradenitis suppurativa; RBP, RNA-binding protein.

SEED Therapeutics is amongst those who are nevertheless working to let other E3 ligases shine. Its lead programme harnesses the DCAF15 ligase to degrade the splicing factor RBM39. This programme builds on over 25 years of research on aryl sulfonamide small molecules, adds SEED president and CSO James Tonra. In 1999, Eisai reported that its indisulam stalls cell cycle progression in cancer cells – prompting a failed attempt to develop the drug as a chemotherapy candidate. In 2017, researchers reported that this class of drug in fact acts by remodelling DCAF15 to ubiquitinate RBM39, a protein that regulates the splicing of mRNA precursors.

Armed with a better understanding of RBM39 biology, SEED is set to advance an optimized RBM39 degrader into the clinic next year.

“There’s a big opportunity for RBM39 degraders in the clinic for new indications, in everything from neuroblastoma to liver cancer,” says Tonra.

Mullard, *Nature Reviews Drug Discovery* (2024)

BeyondSpring

Highly Experienced in-House R&D Team

Discovery Labs, City of Science, King of Prussia, PA

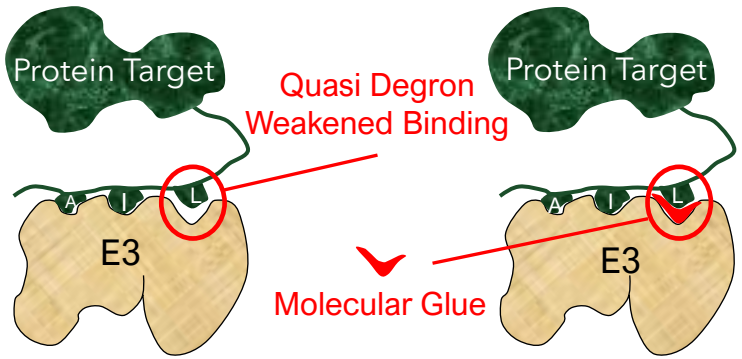
- 10,000 sq. ft. headquarters with 7,000 sq. ft. state-of-the-art laboratory
- All crucial discovery work is conducted by internal research team

Highly Experienced Internal R&D Team

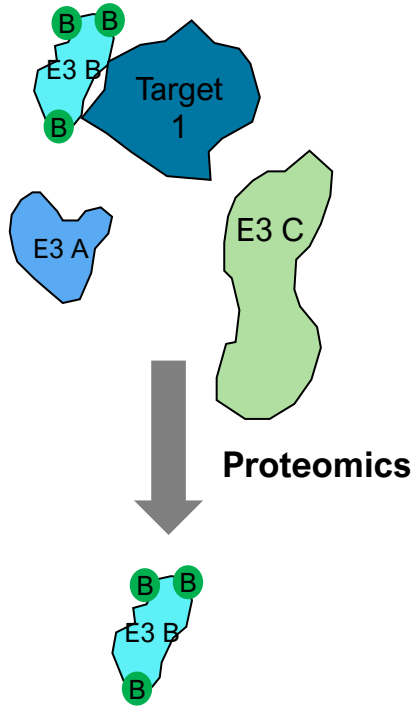
- >100 years combined small molecule hit-to-lead and lead optimization work
- >60 years Medicinal Chemistry and SBDD work
- >60 years DMPK work
- >60 years nonclinical development/safety work
- **>40 INDs filed**
- **>12 NDAs achieved**, including multiple biologics and the small molecules Paritaprevir, Glecaprevir, XERMELO, REZUROCK, GV-971 and Modafinil

Multi-Dimensional and Proprietary Platform for E3 Selection

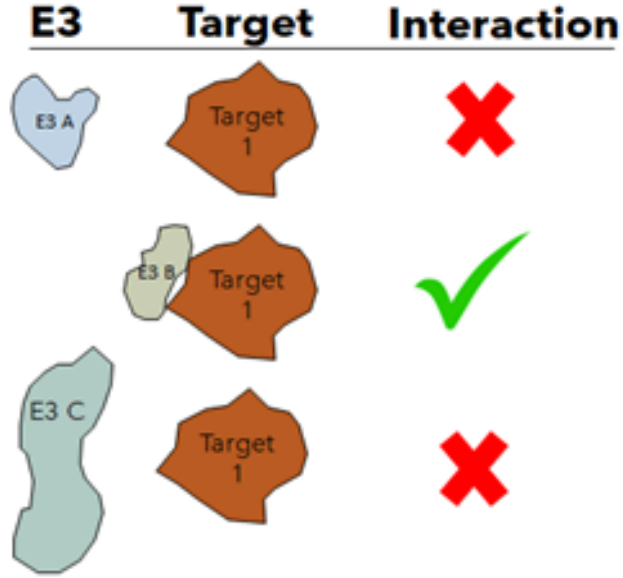
Quasi-Interface Analyses



LumID: identify the right E3 near POI in live cell



Basal Affinity Validation

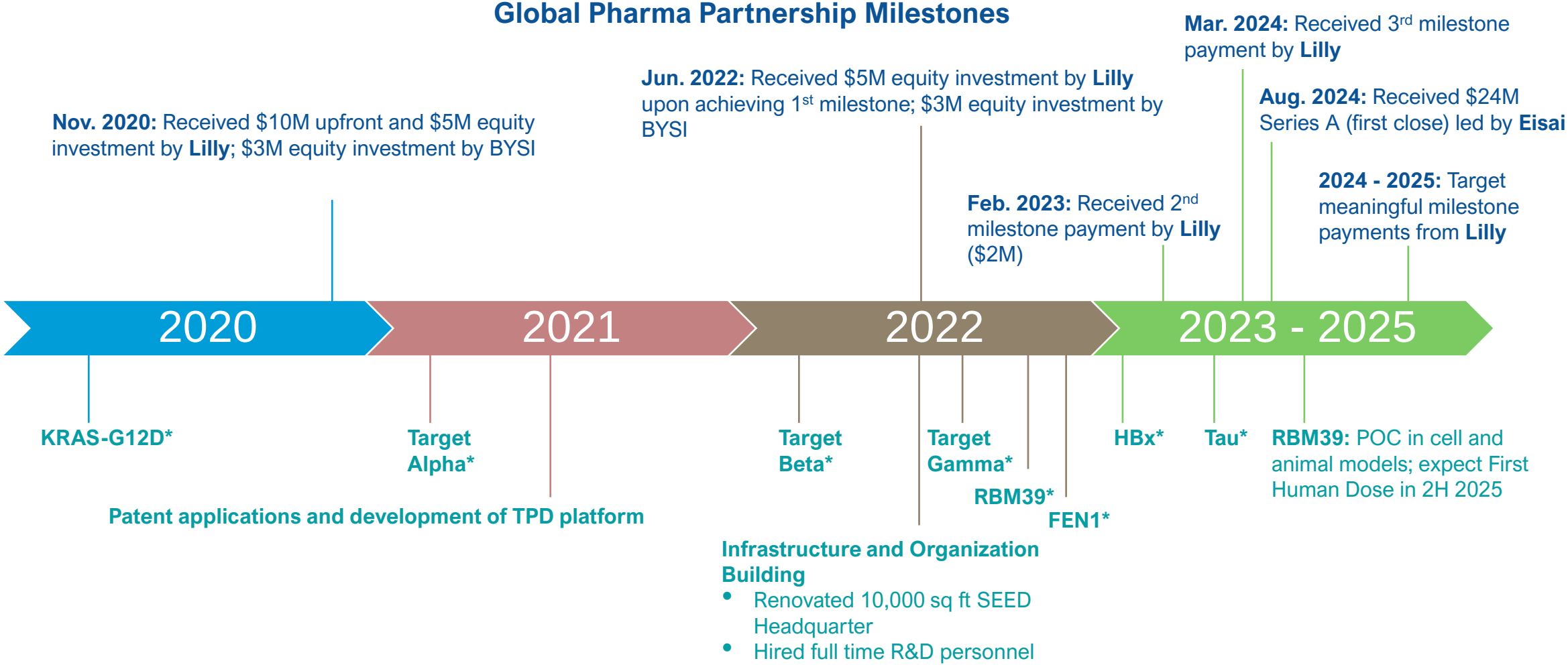


SEED has access to a curated library of over 60 E3 Ligase from SEED's laboratory and from the laboratories of Co-Founders Ning Zheng and Michele Pagano

POI: Protein of Interest

Productive Development History

Global Pharma Partnership Milestones



SEED Internal Program Milestones

*Program initiation

Diversified and Fast Progressing Pipeline

Indication	Target Protein	Target Selection	E3 Ligase ID	Molecular Glue HTS	Lead ID	IND Candidate	IND Filing
Oncology	RBM39						FHD: 2H 2025
	KRAS-G12D						
	Target Beta						
	FEN1						
Neurodegeneration	Target Alpha						
	Tau				In Vivo Activity Plan: 1H 2025		
	Target Delta						
Immunology	Target Gamma						
Antiviral	HBx						

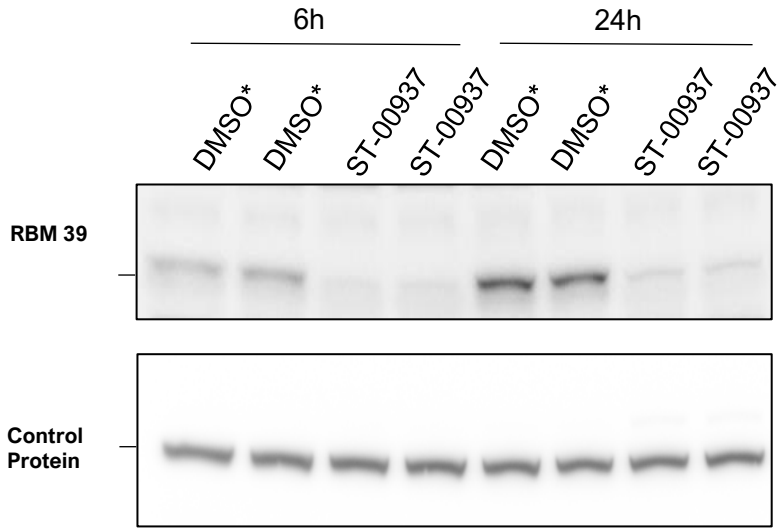
*: SEED owns global IP on all programs except for two joint programs with Eli Lilly and Company

RBM39 Degrader: Received FDA Orphan Designation, Expected IND in 2025

Program Summary

- **POI**: RNA splicing factor RMB39; **E3**: DCAF15; **MOA**: RMB39 degrader MG
- **Target indications**: Biomarker selected colon cancer, prostate cancer, neuroblastoma, and others
- **Development stage**: IND candidate; FHD in 2H 2025
- **Differentiation**: Our novel degrader demonstrates superior anticancer potency in cell line, improved pk, brain permeability, and safety profile compared to competitors
- **Preclinical Success**: Demonstrated potent anti-cancer activity; complete tumor regression as monotherapy in multiple cancer models
- SEED owns **global rights**
- Data supports robust anti-cancer activity with minimal toxicity, highlighting potential for clinical translation

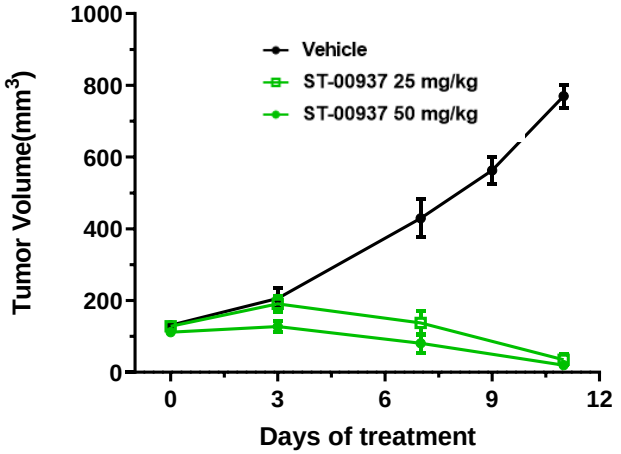
POC: RBM39 Degradation in Cell Line



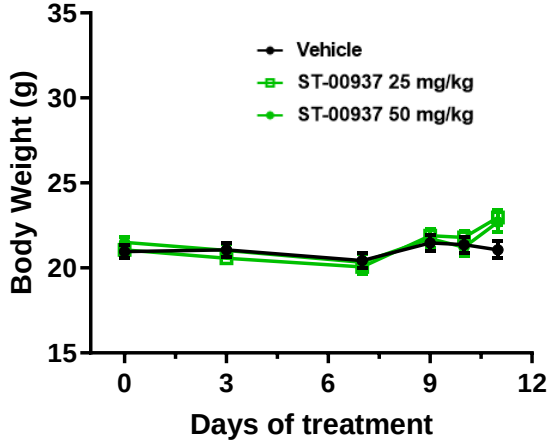
*Vehicle

Human colorectal cancer cell line

In Vivo Efficacy of ST-00937: Complete Tumor Regression Observed



Good In Vivo Safety: No Weight Loss



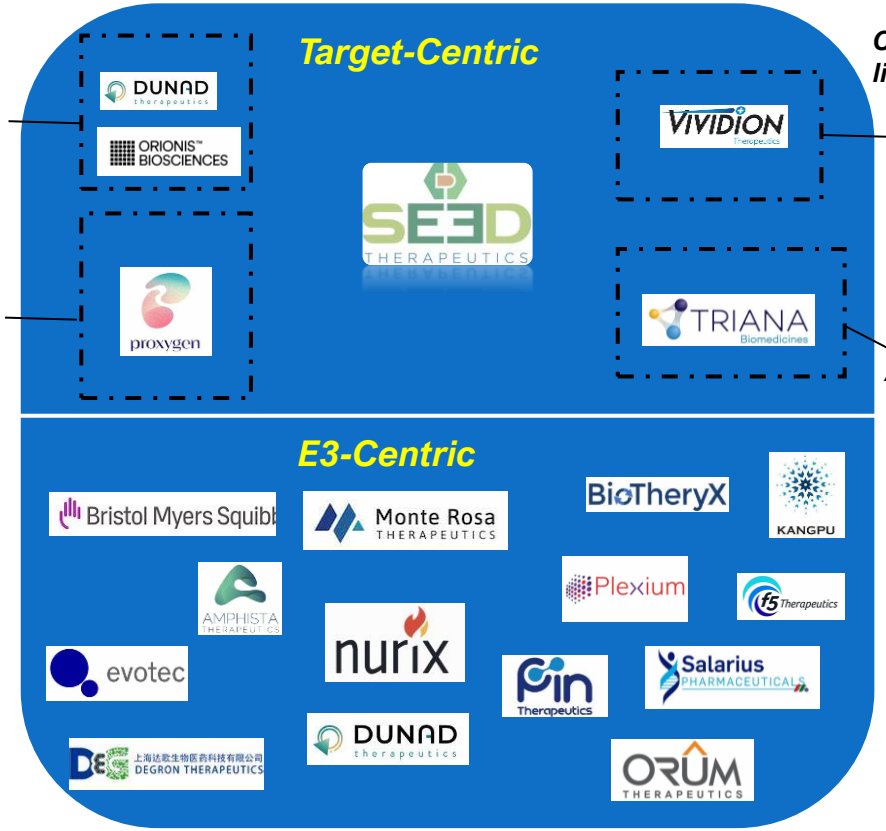
Colorectal xenograft in immunodeficient mice (Oral dose, twice daily)

BeyondSpring

TPD: a High Value and Novel Therapeutic Modality

Allosteric effect based
- Not MG selective
- Lack of evidence for TPD through small molecule-induced allosteric changes in protein structure

Cell-based HTS assays
- May not be MG selective
- Difficult to screen at higher compound concentrations that may be required



Covalent binder libraries
- Lack of evidence of target specificity
- No consideration for importance of Basal Interaction

AI-based approach
- Lack of evidence for applicability to Molecular Glue discovery from scratch and E3 selection

All top 20 global pharma have TPD programs internally and / or through collaboration

- **Discovery stage TPD assets** has been commanding **$35 - $60 million** upfront and **$500 million - $5 billion** milestone payment. Notable transactions include licensing and R&D collaboration deals between
  - ✓Genentech and Orionis; Genentech and Monte Rosa
  - ✓Astellas and Cullgen
  - ✓BMS and Evotec
  - ✓Genentech and Jemincare
  - ✓Bayer's acquisition of Vividion for **$1.5 billion** in 2021
  - ✓Merck's acquisition of Peloton for **$1.1 billion** in 2019

- **Pre-IND/ IND stage TPD assets** has been commanding **$100 - $300 million** upfront and **up to $2 billion** milestone payment. Notable transactions include licensing deals of
  - ✓Lilly from Foghorn
  - ✓Sanofi from Kymera
  - ✓GSK from IDEAYA
  - ✓BMS and Orum

- **Clinical stage TPD asset** (Phase I & II) have been commanded **$150 - $650 million** upfront, **$350 million** equity investment and $2.1 billion milestone payment in collaboration between
  - ✓ Pfizer / Arvinas
  - ✓ Novartis and Monte Rosa

Investment Highlights

Plinabulin: Safety & Efficacy	Lead Asset Plinabulin: >700 cancer patients treated with good tolerability; Positive Phase 3 data in 2/3L NSCLC, EGFR wild type
Plinabulin Potential	Plinabulin: Dual Benefit in anti-cancer and prevention of CIN; Potential in re-sensitizing in PD-1/PD-L1 progressed patients in multiple cancers
SEED: Novel TPD Platform & Pipeline	SEED: 9 Disclosed Pipeline Assets with 1 expected to enter IND in 2024
Premier Partnerships	SEED: Investments and R&D Collaborations from Eli Lilly and Company and Eisai
Intellectual Property	Strong IP and technology protection

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