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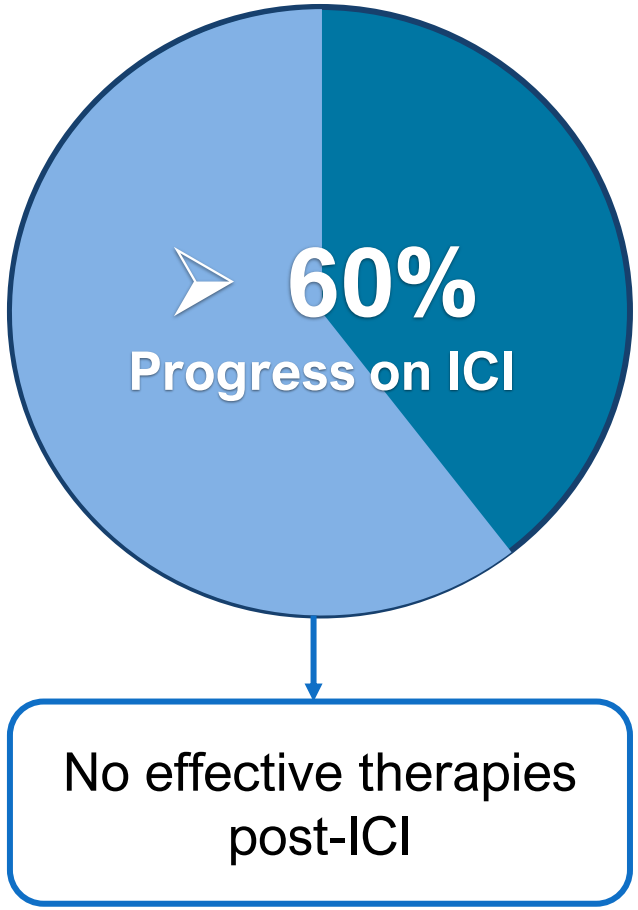
Investment Highlights

Plinabulin Favorable Safety Profile	Over 700 Cancer Patients Treated with Good Tolerability
Anti-cancer Efficacy	Positive Phase 3 study in 2L/3L NSCLC with Overall Survival Benefit: 1. durable anti-cancer benefit in doubling 2-year, 3-year OS rate 2. enables more chemo doses and reducing chemotherapy-induced neutropenia
Target ICI Failure & Potential Frontline	Promising efficacy data in ICI (immune checkpoint inhibitors) combo - Plinabulin + PD-1/L1 Inhibitor + radiation/chemotherapy - in patients with various cancers after ICI-failure
SEED: Novel TPD Platform & Pipeline	SEED: 9 Disclosed Pipeline Assets, with lead oncology asset just cleared US FDA for IND; Investments and R&D Collaborations from Eli Lilly and Eisai
Intellectual Property	Strong Global Patent Protection for Plinabulin and SEED TPD Platform and Pipeline

Post-ICI Landscape: Massive Unmet Medical Need, No Approved Therapies



Immune Checkpoint Inhibitors (ICIs) Have Transformed Cancer Care

A $60B Sales/year Success Story with a Critical Gap

- Approved in 20+ cancer indications
- Nearly $60B in global annual sales
- Have redefined first-line treatment in NSCLC and other solid tumors

Current Options are Limited and Toxic

- >60% patients develop “Acquired Resistance” to ICIs

(due to “T cell exhaustion” and/or “antigen presenting cell (APC) pathway mutation”)[1] After progression, ICIs are no longer effective

- Current options include chemotherapy, which is associated with severe neutropenia

Urgent Opportunity

- No approved therapies specifically address ICI resistance/progression
- Significant clinical and commercial opportunity

1. Memon et al. Cancer Cell 42, 209–224 (2024).

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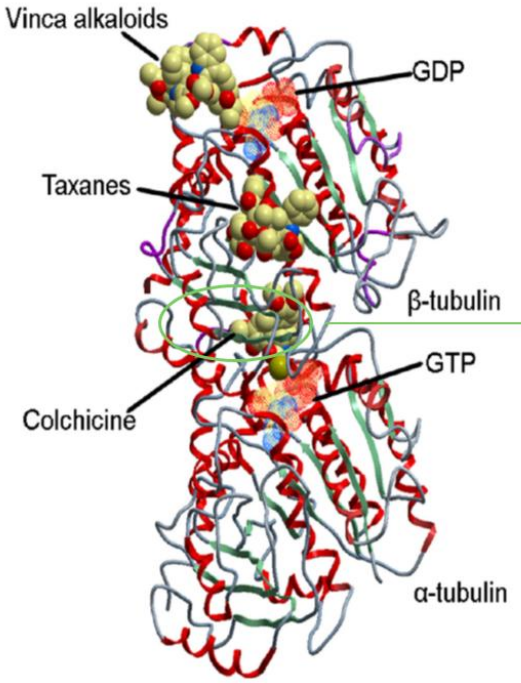
Plinabulin: First-in-class Late-Stage Clinical Asset for Cancer Treatment

Plinabulin: Induces Innate and Adaptive Immunity via Dendritic Cell (DC) Maturation

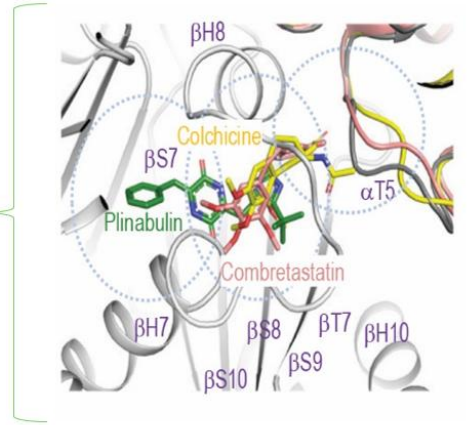
By depolymerizing microtubules, plinabulin releases and activates immune-defense protein GEF-H1

Plinabulin is a unique tubulin binder and does not change tubulin dynamics

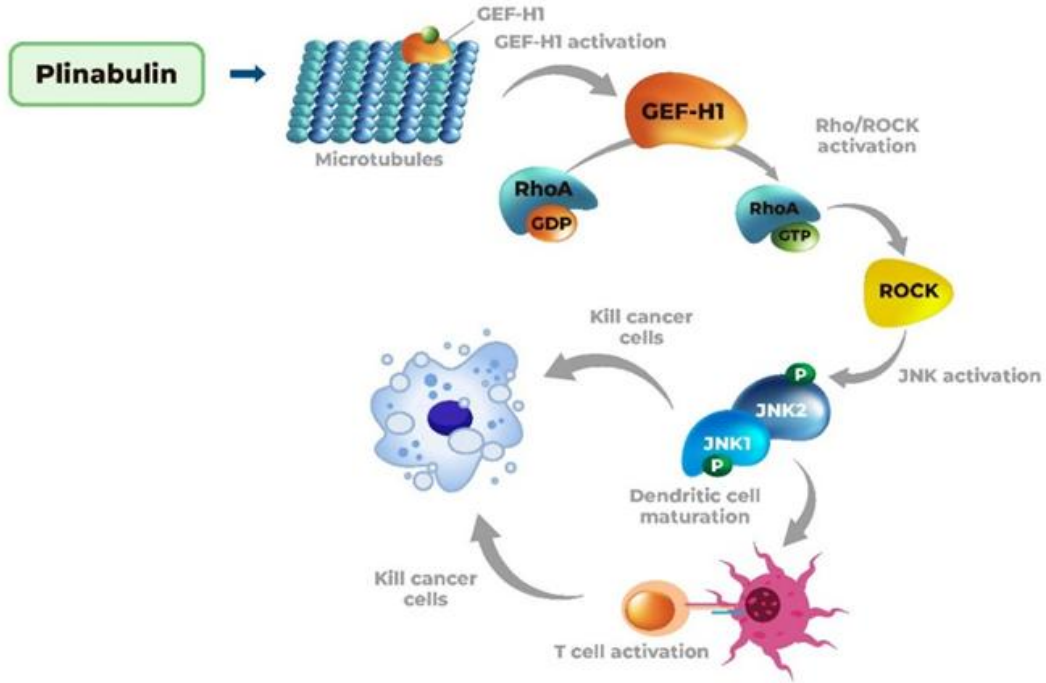
Tubulin Binding Sites



Plinabulin Binds to β-Tubulin, Near the Colchicine Site[1]



Plinabulin Novel Target GEF-H1 activates RhoA/ROCK pathway, leading to DC Maturation[2]



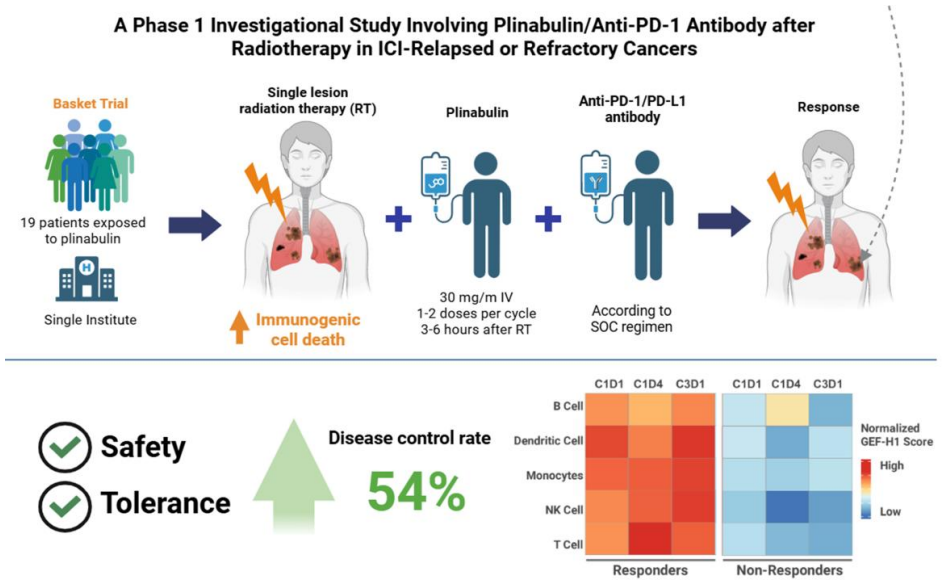
[1] La Sala et al., Chem 5(11): 2969-2986 (2019)

[2] Kashyap et al., Cell Reports 28(13): 3367-3380 (2019)

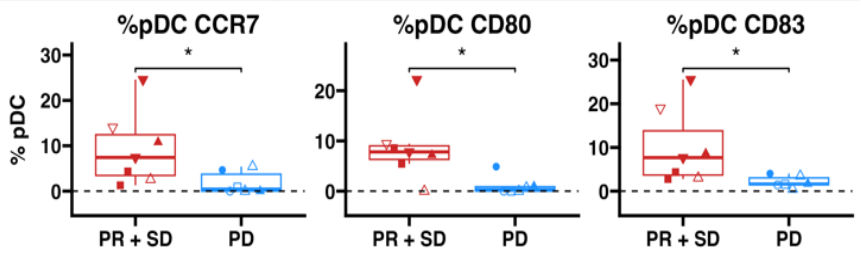
Plinabulin-Responding Patients Show Rapid DC Maturation in the Peripheral Blood

MD Anderson Collaboration, Published in "Med" Cell Press in June 2025

CCR7, CD80 and CD83 are rapidly upregulated at cycle 1 Day 4 in responding (PR + SD) patients



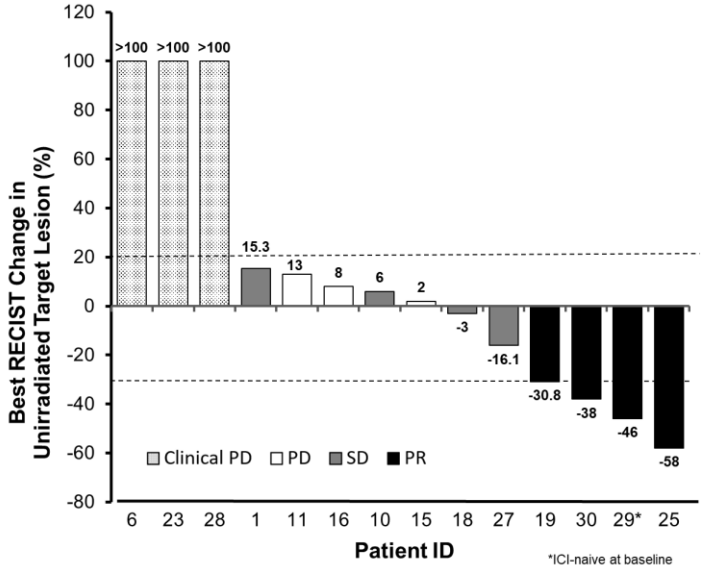
Dendritic Cell Maturation & Migration



Phase 1 Data:

Plinabulin triple combination:

23% ORR, 54% DCR



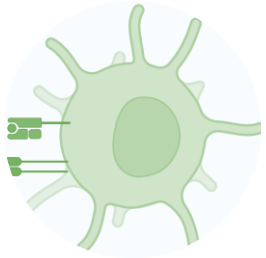
14 evaluable patients:

NSCLC (#1, #19, #29*);
Merkel cell (#11);
RCC (#16, #18, #28);
FL-HCC (#10); CRC (#15);
HNSCC (#23, #27);
Hodgkin (#25, #30);
Melanoma (#6)

Lin et al., Med, Online now, 100752, June 27, 2025

Plinabulin's Immunomodulation and Neutropenia-Mitigating Activities Position it as a Valuable Agent to Target "Acquired Resistance" in ICI Failure

Plinabulin MOA: DC Maturation, M1 Macrophage Polarization, and Tumor Vasculature Targeting



Antigen Presenting Cell (APC)

Plinabulin induces

DC maturation +

M1 Polarization

Enhanced antigen presentation and T cell priming

Tumor Vasculature

Plinabulin targets

tumor vasculature

Vascular Normalization

Improves safety*

Plinabulin **reduces chemotherapy-induced neutropenia**

Improved therapeutic index of chemotherapy-based regimens

Target "Acquired Resistance" to ICI

Extends chemo therapeutic duration and improves anti-cancer benefit

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

*Mechanism validated in preclinical and translational studies (Cell Reports 2019; Med 2025).

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Plinabulin Clinical Studies in Multiple Cancers

>700 cancer patients treated with Plinabulin with good tolerability

	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) - OS, PFS, ORR benefit [1]
Late stage	**CIN Prevention**	Plinabulin alone or + Pegfilgrastim						Studies 105 & 106 [2, 3] (PROTECTIVE-1 & PROTECTIVE-2)
	NSCLC (2L/3L, progressed on PD-1/L1 Inhibitor	Plinabulin + Pembrolizumab + Docetaxel						Study 303
	ES-SCLC (1L)	Plinabulin + Pembrolizumab + Etoposide / Platinum						Study 302
	Multiple cancers Failed PD-1/L1 Inhibitor	Plinabulin + PD-1/PD-L1 + Radiation						THE UNIVERSITY OF TEXAS MD Anderson Cancer Center [4]

Plinabulin's mechanism is not restricted to Lung Cancer; other solid tumors may potentially benefit

1. Han et al., **Lancet Resp Med** 12(10): 775-786 (2024), 2. Blaney et al. **JAMA Oncol** 6(11): e204429 (2020); 3. Blaney et al. **JAMA Network Open** 5(1): e2145446 (2022);
4. Lin et al., Med, Online now, 100752, June 27, 2025

Plinabulin Improves Overall Survival and Enhances Safety in 2L/3L NSCLC, EGFR WT (Global Phase 3 study - Dublin-3 Study)

- The Lancet Respiratory Medicine (Sept 9, 2024)
- BeyondSpring Delivers Oral Presentation at ISLAC 2024 World (globenewswire.com)

Docetaxel Remains a Global Standard of Care (SOC) in Post-ICI NSCLC

Docetaxel Overview

- Approved >25 years ago
- Remains the NCCN-recommended standard of care for 2L/3L NSCLC with no targetable alterations
- Used after progression on anti-PD-(L)1 antibody ± chemotherapy
- Used in real world practice across U.S., EU, Japan, and China

Limitations

- Median OS: ~9 months
- 40% experience severe neutropenia

Industry-wide Phase 3 Trials Summary

- 7 global trials including ADCs and anti-PD-(L)1 combos failed to improve OS vs. docetaxel[1]
- PRAGMATICA-LUNG (SWOG S2302) — ASCO 2025
  - ➢ Enrolled advanced NSCLC patients post-ICI (≥84 days ICI treatment) + platinum chemo
  - ➢ ITT population (n=838) randomized 1:1
  - ➢ OS:
    - Ramucirumab + pembrolizumab: 10.1 months
    - Standard of care: 9.3 months
  - ➢ OS Hazard ratio: 0.99 (p=0.46); no statistical OS benefit[2]

1. **Malinou J et al., ASCO 2024**; 2. Dragnev KH etal. ASCO 2025

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

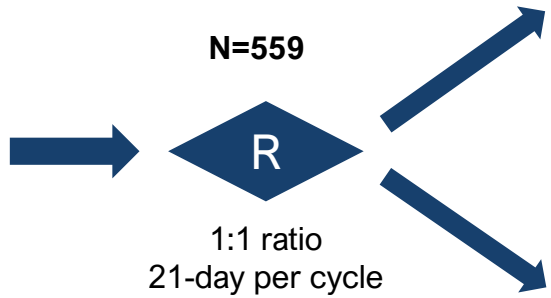
Overall survival (OS)

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)

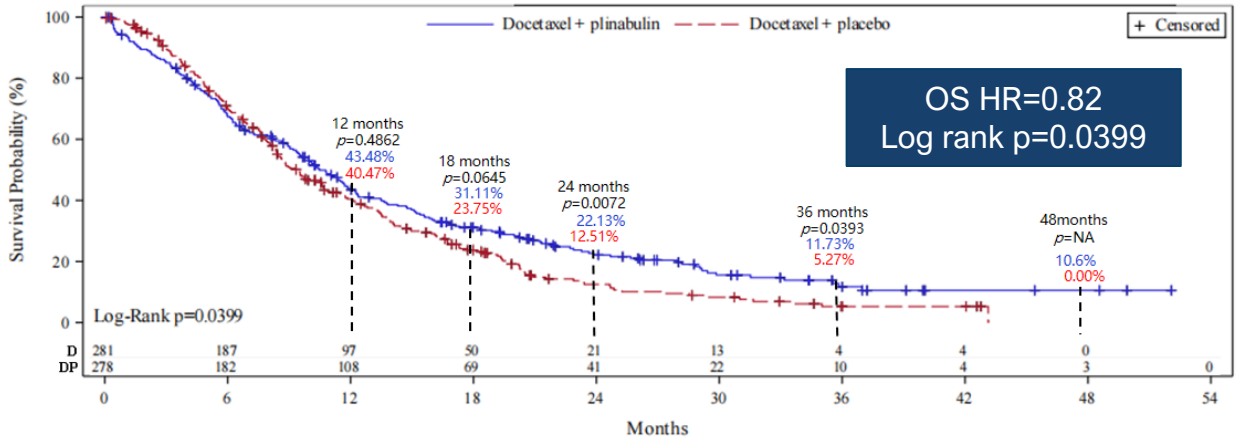
D:
Docetaxel
(75 mg/m2, day 1)
+ Placebo (day 1, 8)

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

Plinabulin + Docetaxel vs. Docetaxel (n=559) Met its Primary Endpoint (OS, HR 0.82) and Secondary Endpoints of PFS, ORR, and Grade 4 Neutropenia Reduction

Plinabulin and Docetaxel Showed Significant Improvement in Long-term OS Rate

- Double 2-year, 3-year OS Rate

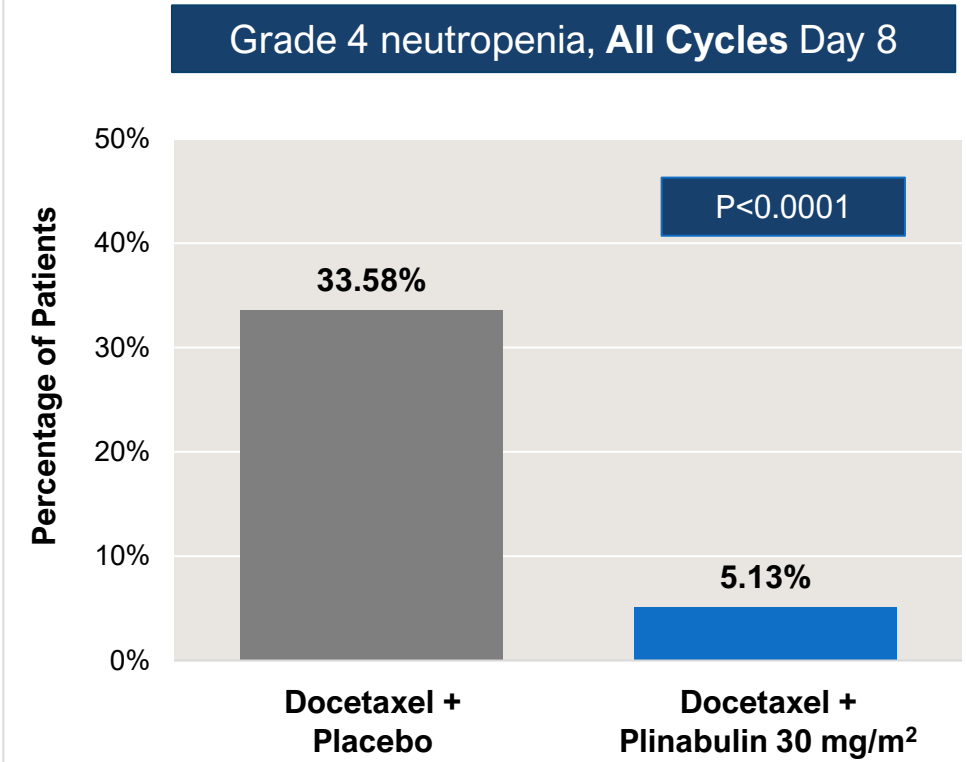


Treatment	Subjects	Event	Censored	Median (95% CI)	HR (95% CI)
Docetaxel + placebo	281	230 (81.9%)	51 (18.1%)	9.40 (8.38,10.68)	
Docetaxel + plinabulin	278	214 (77.0%)	64 (23.0%)	10.49 (9.34,11.87)	0.822(0.681,0.991)

	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)

LANCET Res Med 12 (10), 775-786 (2024)

Plinabulin Significantly Reduced Grade 4 neutropenia of Docetaxel



Similar results for Grade 4 neutropenia on Cycle 1 Day 8

- Day 8 is ANC Nadir for Docetaxel

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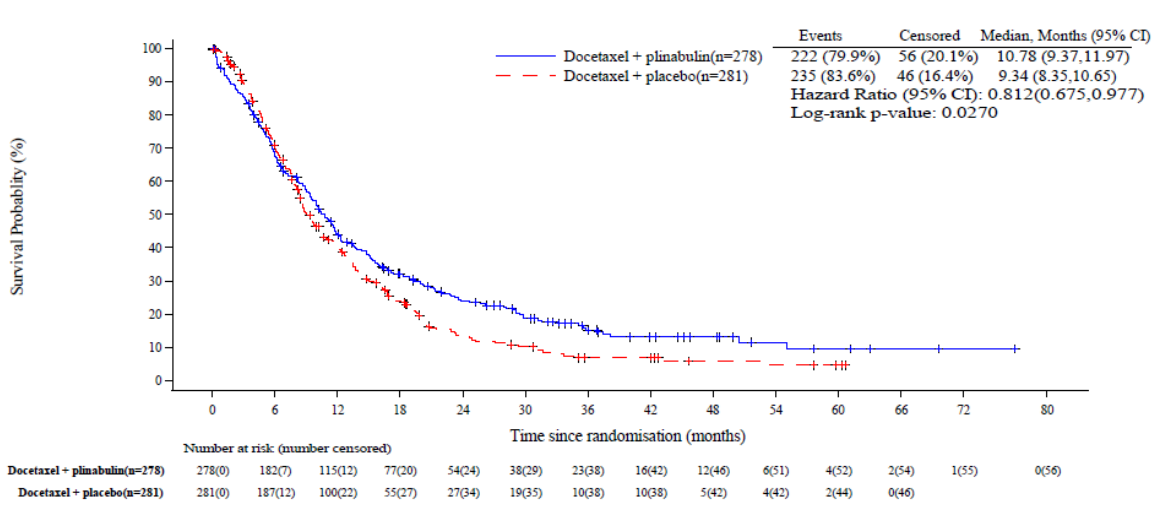
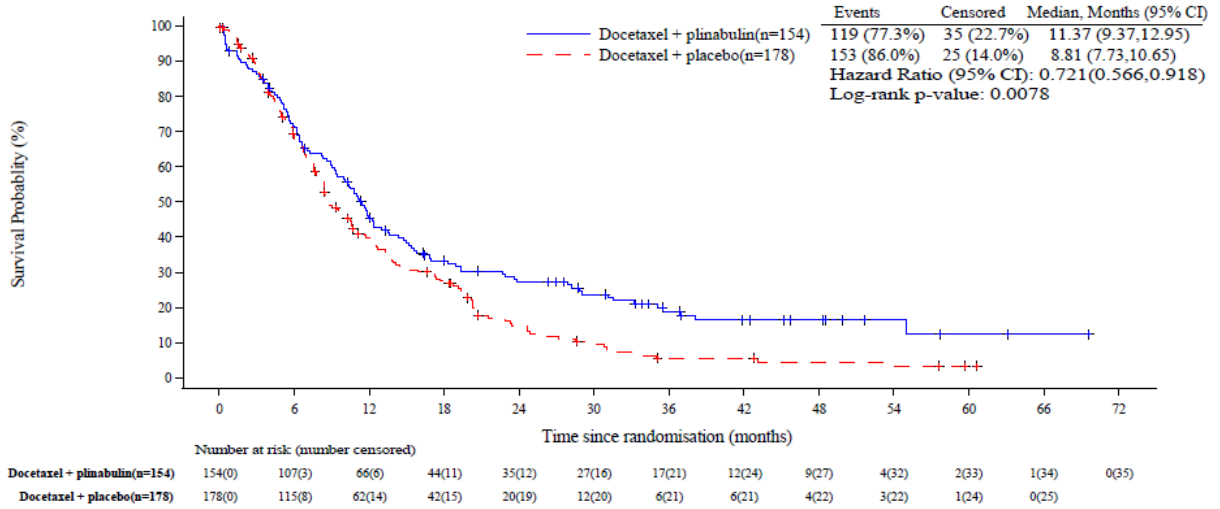
Consistent OS Benefit in 24-month follow up after Database Lock

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: Plinabulin + Docetaxel with Well-tolerated Safety Profile

	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 + Docetaxel Improved Overall Survival vs. SOC Docetaxel in 2L/3L NSCLC

Plinabulin + docetaxel improved overall survival and enhanced safety with positive benefit/risk ratio in 2L/3L NSCLC (EGFR wild type) patients vs. Docetaxel

Efficacy

- Significant overall survival benefit and significant improvement in ORR and PFS in ITT population
- Better survival benefit in non-squamous patient population

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

303 Study: A Phase 2 IIT Study of Pembrolizumab (Pemb) plus Plinabulin (Plin) and Docetaxel (Doc) in Metastatic NSCLC Patients (pts) Who Progressed on Prior Immune Checkpoint Inhibitor

Presentation at ESMO (Sept 2024), SITC (Nov 2024), and ASCO (May 2025)

IIT Phase 2 303 Study: 2L/3L Metastatic NSCLC, All Progressed on PD-1/L1 Inhibitor

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

- Pembrolizumab 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.

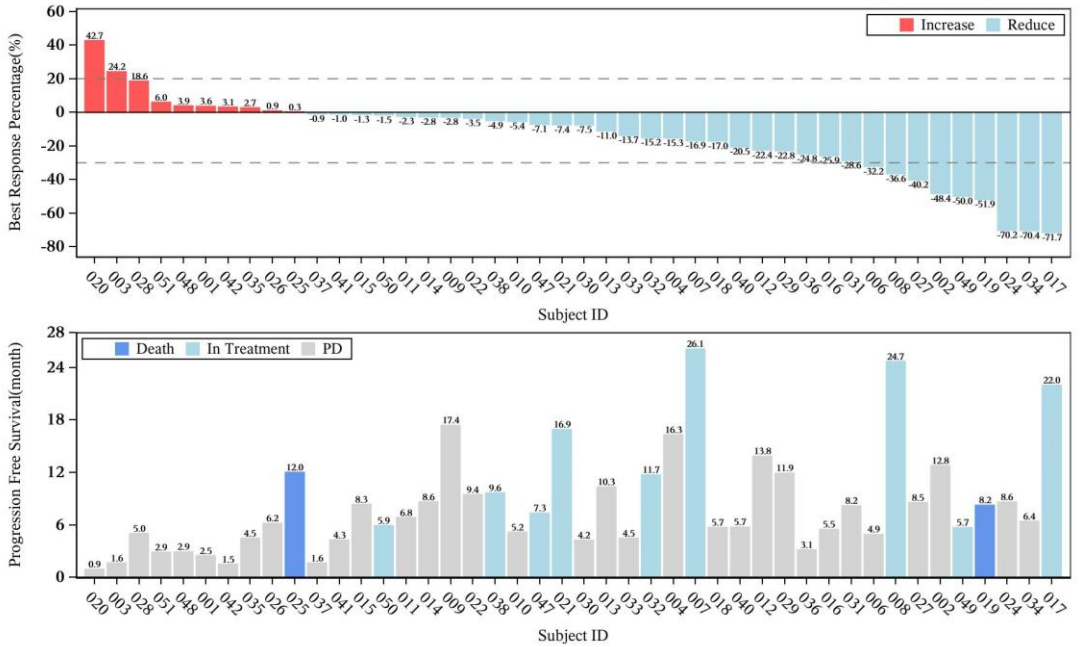
Stage 2: Total enrollment of 47 patients. If > 8 patients with PR, the study meets its objective.

303 Study Efficacy (cut-off date on May 16, 2025) – 2025 ASCO Presentation

Updated Analysis: 47 patients (ITT)
median follow-up time: 12.7 month (m)

Primary Endpoint (n=47)	
Confirmed ORR (RECIST 1.1)	**18.2%**
Secondary Endpoint	
Median PFS (RECIST 1.1)	**6.8 months**
Median OS	Not reached
Median DoR (RECIST 1.1)	7.2 months
Disease Control Rate (DCR) (PR + SD > 4 months)	**77.3%**
6 months PFS%	56.0%
15 months OS%	**78.0%**

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



*25/28 – 2 withdrawn after first dose

303 Study: Safety Summary

Treatment Emergent Adverse Events (CTCAE 5.0 ≥ Grade 3)

SOC PT	Pemb + Plin + Doc (N=47) n (%)
All TRAE, CTCAE >= grade 3	24 (51.1)
Gastrointestinal disorders	7 (14.9)
Diarrhea	4 (8.5)
Ileus	2 (4.3)
Abdominal distension	1 (2.1)
Vascular disorders	7 (14.9)
Hypertension	7 (14.9)
Blood system disorders	8 (17.0)
Neutrophil decrease	7 (14.9)
Decreased white blood cell count	3 (6.4)
Febrile neutropenia	1 (2.1)
Infections and infestations	2 (4.3)
Infectious pneumonia	1 (2.1)
Sepsis	1 (2.1)

SOC PT	Pemb + Plin + Doc (N=47) n (%)
All TRAE, CTCAE >= grade 3	24 (51.1)
Respiratory,thoracic and mediastinal disorders	2 (4.3)
Respiratory Failure	2 (4.3)
Metabolism disorders	2 (4.3)
Acidosis (Related to diabetes)	1 (2.1)
Elevated blood glucose	1 (2.1)
Renal and urinary disorders	1 (2.1)
Acute kidney injury	1 (2.1)
Cardiac disorders	1 (2.1)
Atrial fibrillation	1 (2.1)

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CTCAE, Common Terminology Criteria for Adverse Events; TEAE, Treatment Emergent Adverse Event.

303 Study Summary

Efficacy

- In patients with metastatic NSCLC who had disease progression immediately after clinical benefit with PD-1/L1 inhibitors showed encouraging clinical benefit of **mPFS (6.8 months) and DCR (77.3%),** higher than historical control of SOC docetaxel of around 3.8 months. OS is not reached; **18 months OS rate is 78%.**
- 78% patients used prior Pemb, serving as self-control.

Safety

- The combination is well tolerated.
- Grade 3+ AE includes transient hypertension (14.9%), Diarrhea (8.5%), and Ileus (4.3%) which can be managed by prophylactic medication.

Funding Source: MSD China and BeyondSpring.

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Plinabulin Potential Broad Applicability in Cancer

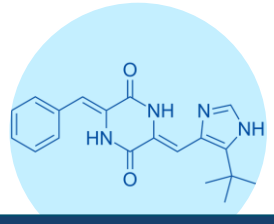
Plinabulin Differentiated Profile

Area	How Plinabulin Is Different
Mechanism	Binds tubulin but activates **dendritic cells**, not just mitotic arrest
Immune Profile	**Bridges innate and adaptive immunity**; lowers MDSCs, increases antigen presentation
Combination Potential	**Synergistic with chemotherapy and checkpoint inhibitors**
Side Effect Profile	Lower neutropenia and bone marrow toxicity; rare bone pain
Tumor Microenvironment	Converts “cold” tumors to “hot”
Multi-Action	**Direct tumor killing + immune priming + vascular disruption**—rare in a single agent

Plinabulin + Docetaxel: Addressing Unmet Needs in 2L/3L NSCLC, EGFR WT, Progression from Prior PD-1/L1 Inhibitors with current SOC Docetaxel

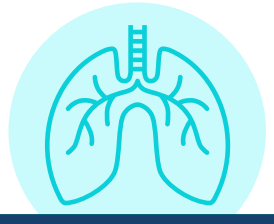
Unmet Need	Severity of Need	Plinabulin Impact
Lack of durable response post-immunotherapy	🔴🔴🔴	🟢🟢🟢 Strong immune re-priming
Poor efficacy of chemotherapy alone	🔴🔴	🟢🟢 Improved OS and PFS
Immune exhaustion, “cold” tumors	🔴🔴🔴	🟢🟢🟢 Converts tumors to “hot”
High chemo-induced neutropenia	🔴🔴	🟢🟢 Reduces Grade 4 neutropenia
EGFR/ALK wild-type population underserved	🔴🔴	🟢🟢 Broad, non-targeted applicability

First-in-class agent Plinabulin: Potentially Transforming Oncology Treatment with Novel Mechanisms and Clinically Meaningful Patient Benefits in NSCLC and Beyond



Unique MOA

A unique tubulin modulator that activates **dendritic cell** maturation and **M1-like macrophage** proliferation which **enables the cancer immunity cycle**



Clinical Success

Successfully demonstrated significant **OS benefit in 2L/3L NSCLC**, as well as **reduction in severe neutropenia,** allowing extended regimen duration

Unmet Medical needs and Market Potential

Clinically enhanced the anti-tumor response to checkpoint inhibitors in combination with radiation or chemotherapy, in **IO-resistant or progressed patient population**

Strong global patent protection

Plinabulin has Granted Patents with **composition of matter to 2036 in over 40 jurisdictions,** including US, EU, Japan, and China

Plinabulin Unique Profile:

1. Easy to use: Day 1 and 8 use in a cycle, intravenous infusion of 30-60 minutes;
2. Clinical Benefit: Overall survival and durable response;
3. Safety Benefit: Reduce AE including chemotherapy-induced neutropenia.

BeyondSpring

SEED Therapeutics: Target Protein Degradation (TPD 2.0) Company

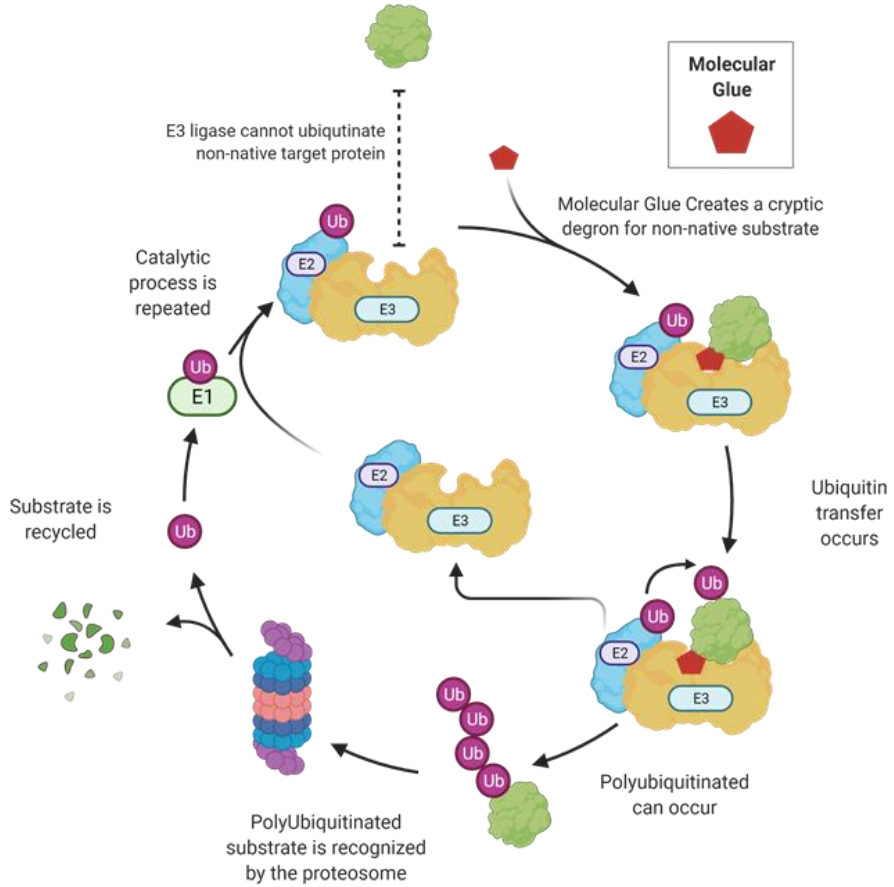
TPD Targets 80% of Disease-Causing Proteins That are Currently Undruggable

Investment Highlights

SEED is a leading Targeted Protein Degradation (TPD) 2.0 company focusing on developing novel “Molecular Glues” (MG) for breakthrough therapeutics

TPD Commercial Potential	Focusing on Molecular Glues (MG) to **address 80% of disease-causing proteins considered "undruggable"** by traditional methods.
World-class Founding Team	SEED Co-Founders **are preeminent global scientific leaders on TPD** with unrivaled insights of E3 structure and biology, including the Nobel Prize Winner Dr. Hershko.
Validated Technology Platform	• RITE3 platform deploys proprietary Quasi-degron, LumID and Basal Affinity tests; • Featured as one of leading companies in TPD in two Nature review papers in 2024; • **RITE3 platform is validated** with the investment and R&D collaboration with global pharma: **Lilly and Eisai**. Potential deal values exceeding **$2.3 billion**.
Rapidly Advancing Pipeline	• Developed **9 programs (6 internal and 3 are partnering assets)** across oncology, neurodegeneration, immunology, and antiviral indications, including 6 internal programs and involving **6 novel E3s**. • Lead internal oncology asset (**RBM39 degrader**) cleared IND with US FDA in August 2025. • Neurodegeneration program (**Tau degrader**) targeting in vivo efficacy around 2H 2025.

Targeted Protein Degradation (TPD) for Disease Proteins That are Undruggable



- **E3 Ligase Expertise**: > 600 E3 ligases in human E3ome, with only 2 structural classes, solved by SEED Co-founders;
- **Target-Centric Approach**: Capable of selecting the right E3 ligase for each disease-causing protein;
- **Ubiquitin Biology Expertise:** Select targeted clinical indication based on ubiquitin biology, pioneered by SEED co-founders;
- **Published & Recognized**: Featured in *Nature Biotechnology* and *Nature Reviews Drug Discovery* in 2024.

Experienced Team with Successful Track Record

Founders

Nobel Prize winner, Pioneers in TPD

Management Team

40 IND and 12 NDA experience

Board Members

Experienced business and legal expert and independent board member from Eli Lilly and Eisai

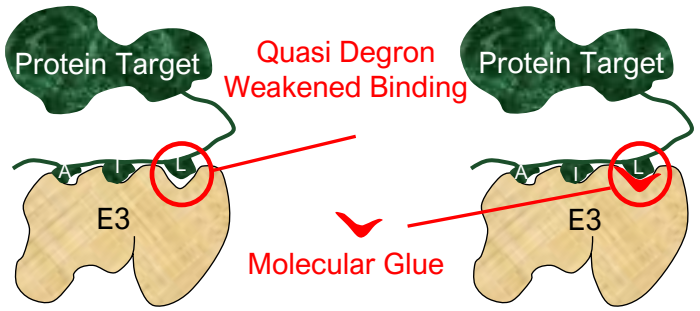
Global Pharma Partnerships: Validating SEED's Leadership in TPD Space

- Research collaboration with **Eli Lilly** on TPD with multiple targets.
- **$10 million upfront**, and a **$10 million** equity investment in series A-2.
- Eligible to receive up to **$780 million** in potential milestones, and **tiered royalties** of sales.

- Series A-3 financing: first close of $24 million from investors led by **Eisai** in August 2024.
- SEED-Eisai Collaboration: SEED receive upfront and milestone payments of up to **$1.5 billion** plus **tiered royalties** upon Eisai's exercise of their exclusive rights under the strategic research collaboration.

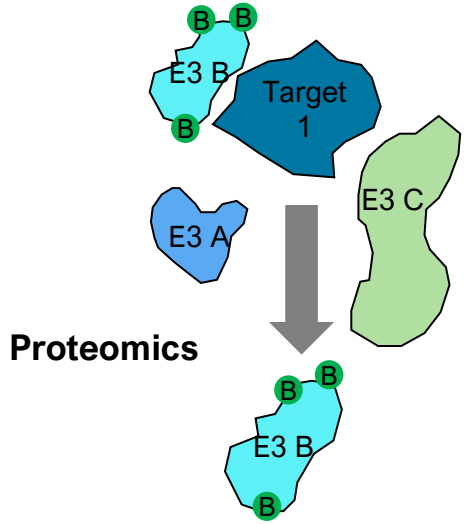
Multi-dimensional Platform RITE3™ to Select E3 for Protein Target*

Quasi-Interface Analyses



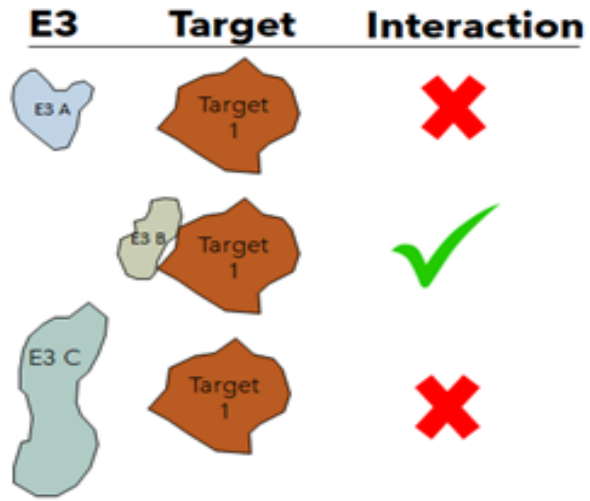
Computational and structural biology

LumID: identify the right E3 near POI in live cell



Cell biology: real-time monitoring of target-E3 interactions

Basal Affinity Validation



Biophysics: distinguishing productive vs. non-specific interactions

Novel E3 Selection for Disease Protein of Interest

↓ High-throughput screening (E3/POI) + Optimization

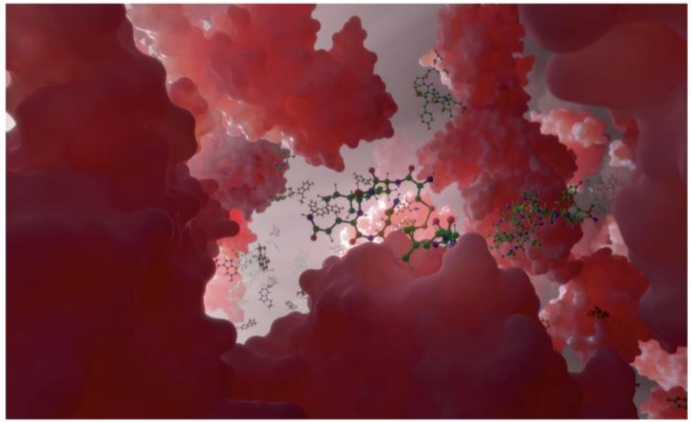
Molecular Glue

*Two Nature Review Papers: Garber, *Nature Biotechnology* 42(4):546-550 (2024); Mullard, *Nature Reviews Drug Discovery* 23 (11):799-802 (2024)

Two Nature Review Articles Naming SEED as One of Leading TPD Companies Focusing on novel E3 ligases developing "Molecular Glues"

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.

CREDIT: SCIENCE LAB / ALAMY STOCK PHOTO

nature biotechnology

Garber, *Nature Biotechnology* (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.

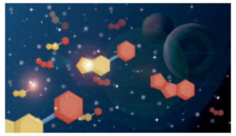
> "This is a hype that actually lives up to its promise"

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.

CREDIT: S.HARRIS/SPRINGER NATURE LIMITED

nature reviews drug discovery

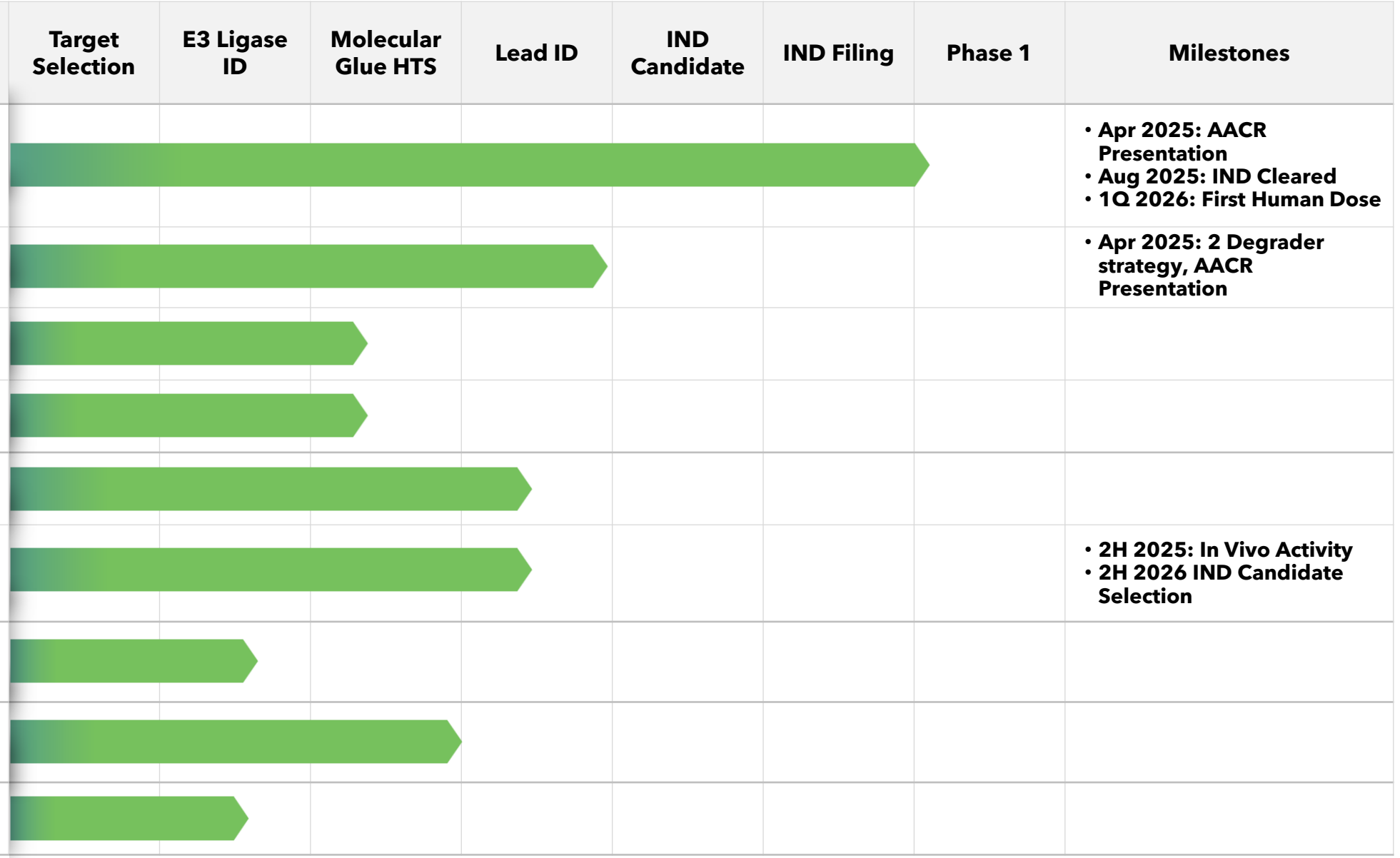
Volume 23 | November 2024 | 799–802 | 799

Mullard, *Nature Reviews Drug Discovery* (2024)

BeyondSpring

Pipeline Targeting Key Undruggable Proteins Across Human Disease

Indication	Target Protein	Milestones
Oncology	RBM39	• **Apr 2025: AACR Presentation** • **Aug 2025: IND Cleared** • **1Q 2026: First Human Dose**
	KRAS-G12D	• **Apr 2025: 2 Degrader strategy, AACR Presentation**
	Target Beta	
	FEN1	
Neurodegeneration	Target Alpha*	
	Tau	• **2H 2025: In Vivo Activity** • **2H 2026 IND Candidate Selection**
	Target Delta*	
Immunology	Target Gamma*	
Antiviral	HBx	



BeyondSpring SEED owns 100% on all programs except for three partnered programs (labeled with *)

Lead Oncology Asset:
Oral Novel RBM39 Degrader

IND Cleared by US FDA in August 2025

RBM39 Degrader: RNA Splicing for Multiple Cancers

The Problem

Cancer cells rely on precise RNA splicing to maintain oncogene expression and survival

Most RNA splicing components are **non-enzymatic and undruggable**

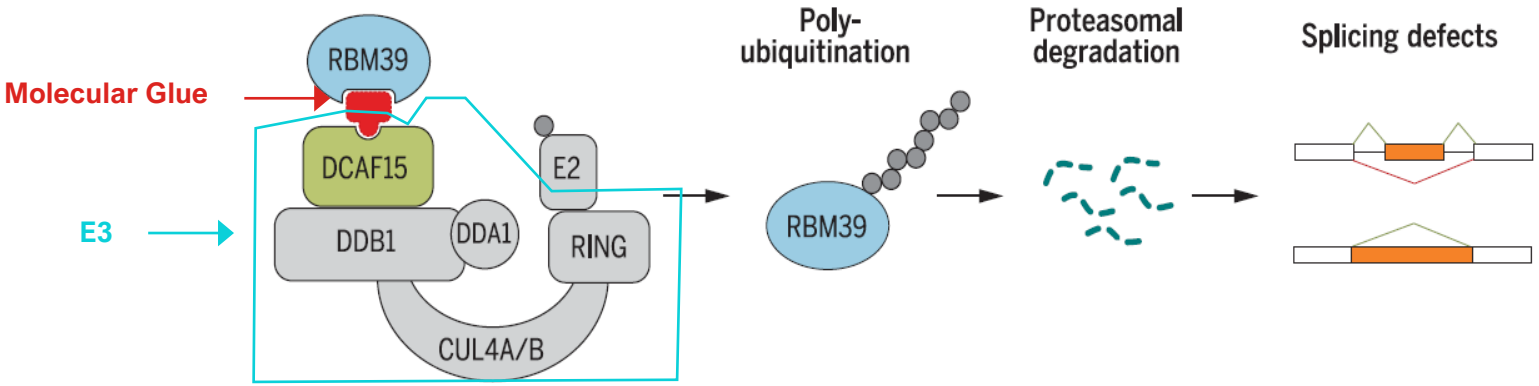
Aberrant splicing is linked to **drug resistance, tumor progression, and immune evasion**

The Solution

RBM39 is a **core splicing factor** essential in a subset of cancers

Targeted degradation via **molecular glues** induces lethal mis-splicing in sensitive tumors

Offers **synthetic lethality** and tumor selectivity with **limited impact on normal cells**



Han et al., *Science*, 2017

RBM39 Degradation Addresses Core Unmet Needs Across Multiple Tumors

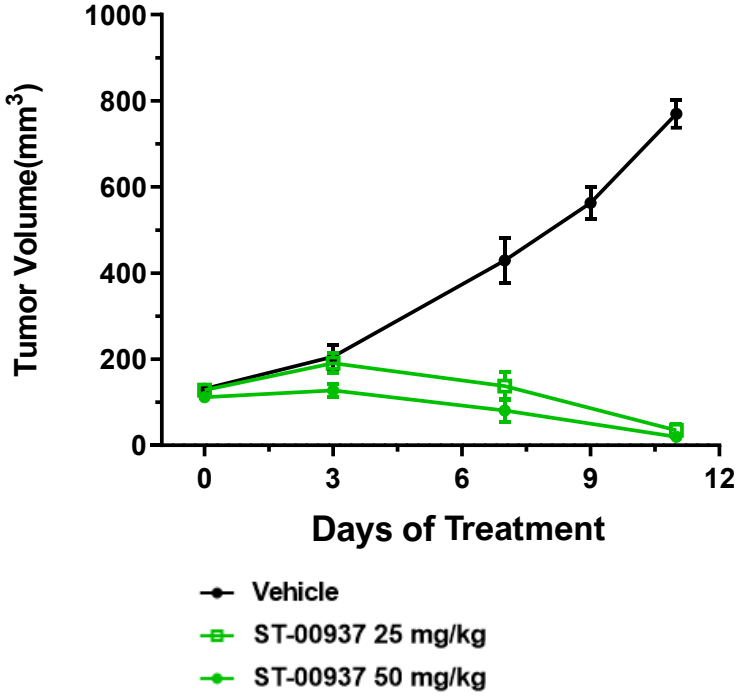
Unmet Need	Ewing Sarcoma	Neuroblastoma	Hepatocellular Carcinoma	Colorectal Cancer	Prostate Cancer	RBM39 Degrader Impact
No effective targeted therapies	🔴 High	🔴 High	🟠 Medium	🔴 High	🟠 Medium	✅ Transcriptional targeting independent of drivers
Therapy resistance and relapse	🔴 High	🔴 High	🔴 High	🔴 High	🔴 High	✅ New mechanism, orthogonal to existing therapies
Lack of predictive biomarkers	🟠 Medium	🔴 High	🔴 High	🔴 High	🔴 High	✅ RBM39 expression and splicing signatures as markers
Late-stage diagnosis	🟢 Low	🟠 Medium	🔴 High	🔴 High	🔴 High	✅ Activity in advanced and metastatic settings
High toxicity of standard treatment	🔴 High	🔴 High	🟠 Medium	🟠 Medium	🟠 Medium	✅ Potential for lower-toxicity regimens
Lack of innovation	🔴 High	🔴 High	🟠 Medium	🟠 Medium	🟠 Medium	✅ First-in-class degrader targeting splicing

RBM39 degradation offers a novel, biomarker-driven, cross-indication strategy that addresses both therapeutic resistance and the lack of transcription-targeted options in hard-to-treat cancers.

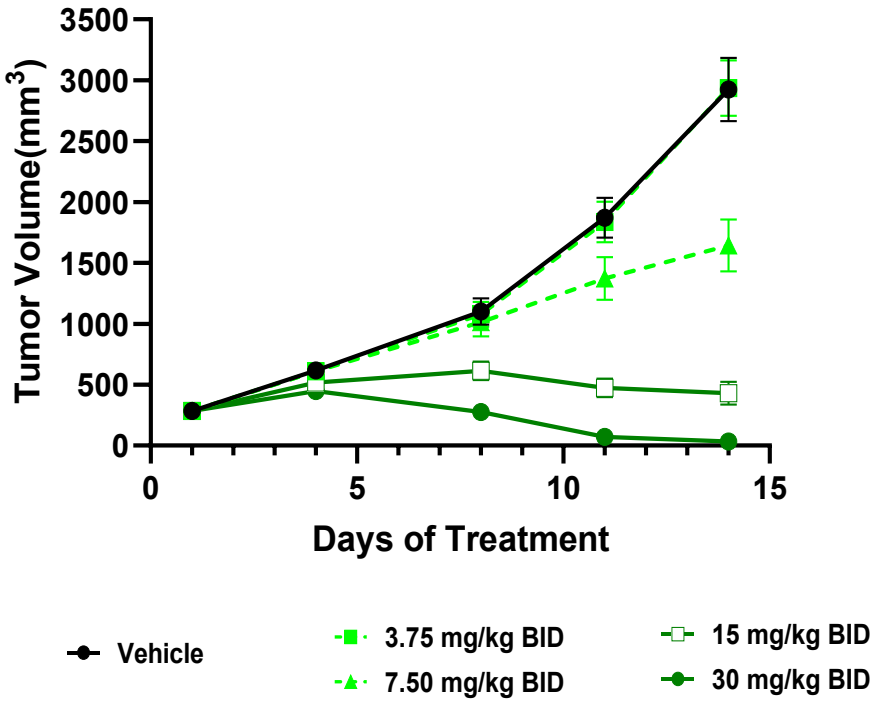
Rational Indication Selection for SEED's RBM39 Degrader

Potentially Target Multiple Cancers Based on Its MoA

Complete Tumor Regression in Colon Cancer Model



Complete Tumor Regression in Ewing Sarcoma
- Rare Pediatric and Orphan Cancer designation by FDA, presentation at AACR 2025

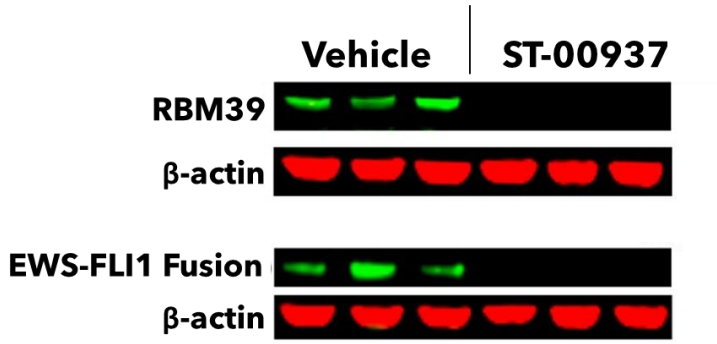


Induce RBM39 Degradation in Tumors and PBMCs in blood After Oral Dosing

Target Engagement Assay for Phase 1 to Achieve Rapid RP2D Dose

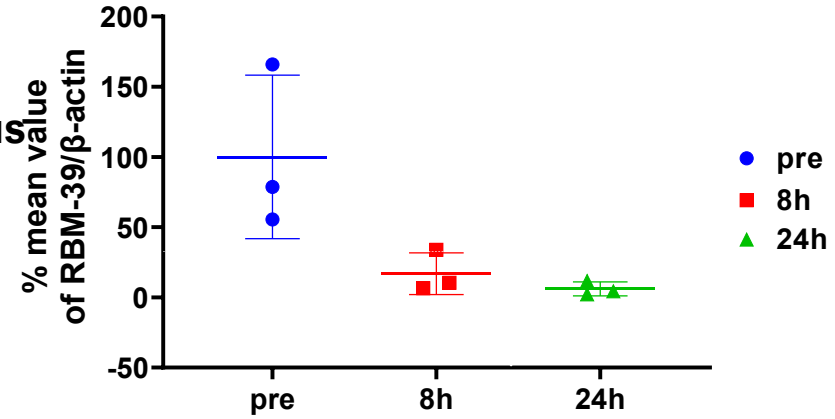
Mice Tumor Model

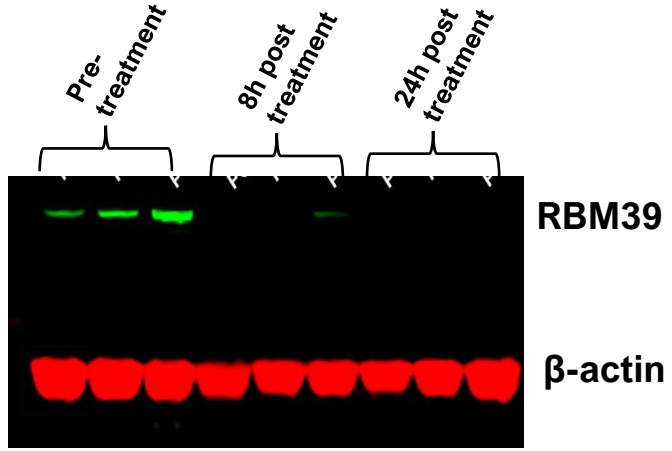
Tumor Protein on Day 3 of Treatment



Normal Cynomolgus Monkey

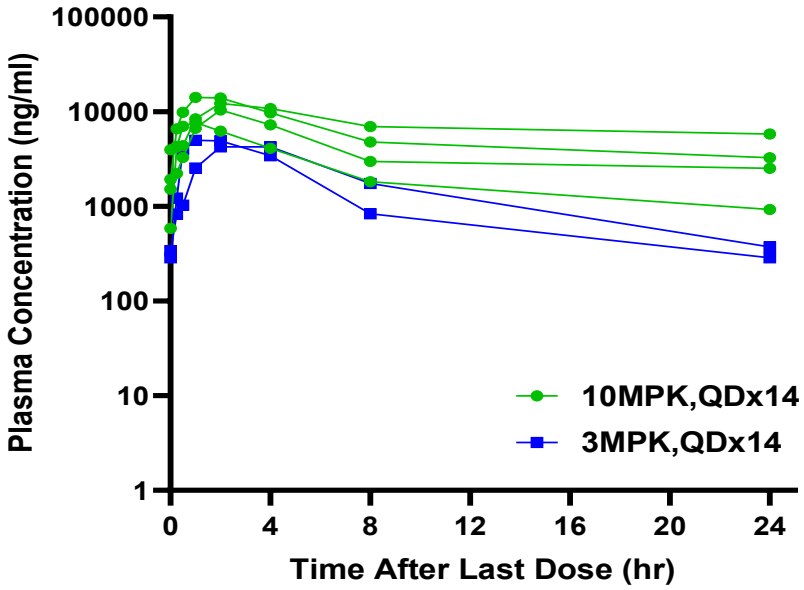
Single 20 mg/kg oral dose, female, fed condition





NHP: Non-human Primate
PBMCs: Peripheral Blood Mononuclear Cells

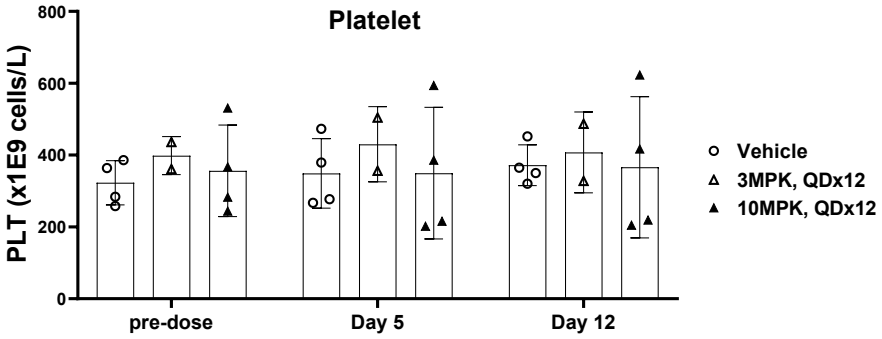
RBM39 Degrader Safety Dose at >10 Times Plasma PK for Anticancer Activities

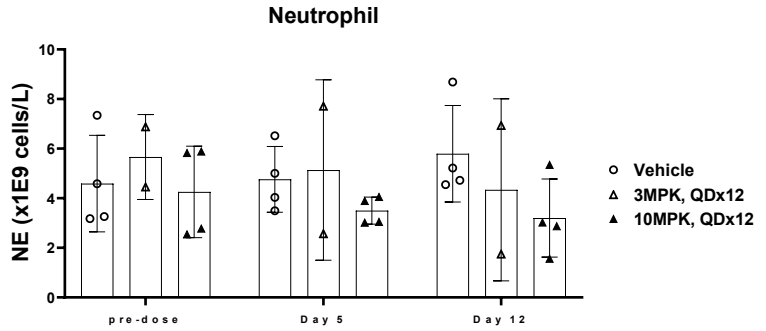


Mean Plasma PK Parameters

Dose	C_{min} (ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24hr}$ (h*ng/mL)
3MPK	321	4615	37902
10MPK	2560	11093	116813

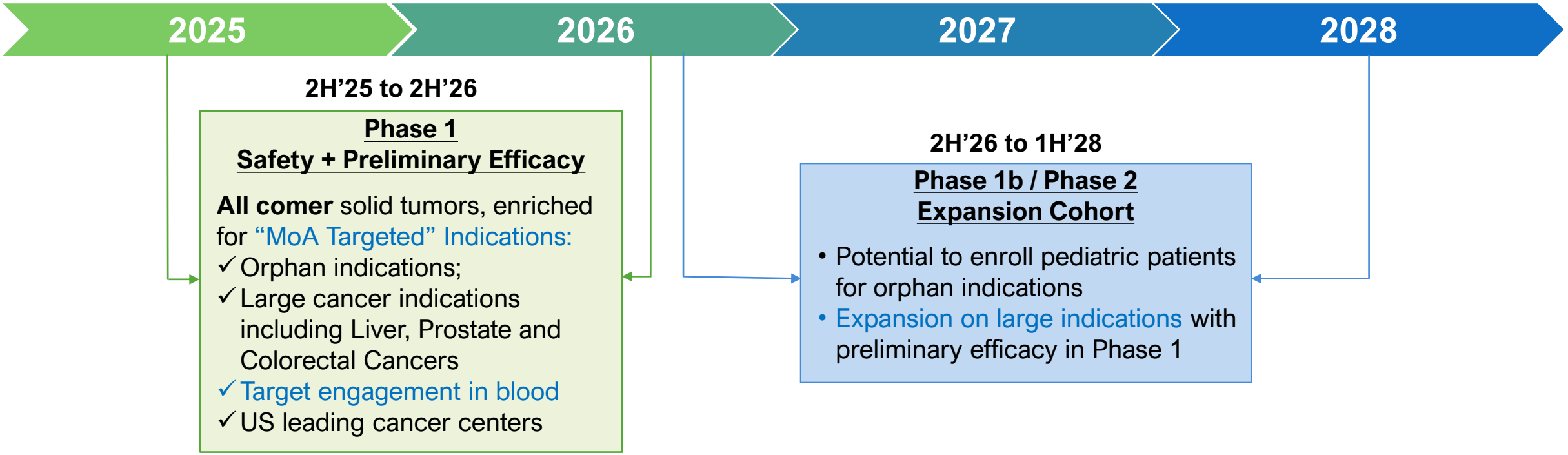
Good Hematological Safety





**Platelet and neutrophil related dose-limiting toxicities reported for prior RBM39 degraders in patients

ST-01156: Clinical Development Plan - “Precision Medicine” Approach



ST-01156: Oral RBM39 Degrader Advancing to Clinical Trials in 2025

Focus on MoA-based Indications; Potential to Accelerate Clinical Development

MoA understanding and preclinical screening on patient-derived models is being used by SEED for **rationale clinical indication selection**

Orphan and large cancer indications to be enriched for “MoA targeted” indications in the first clinical trials to accelerate progress to NDA for responsive cancer types

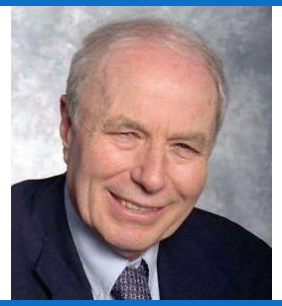
Nonclinical PK/PD and Tox/TK established and set to inform dose escalation to speed progress to dosing regimens with a therapeutic window

Experienced innovative oncology drug development team with investigators from **leading institutions** with patients of all targeted cancer types.

Key Catalysts and Highly Experienced Team

World Class Founding and Leadership Team

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**

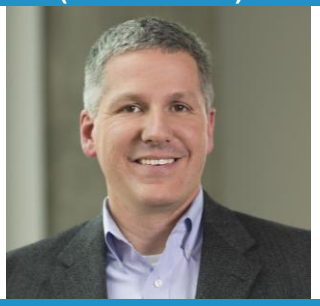
Michele Pagano, MD [+]

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 NDA-ready assets

Bill Desmarais, PhD (CFO & CBO)

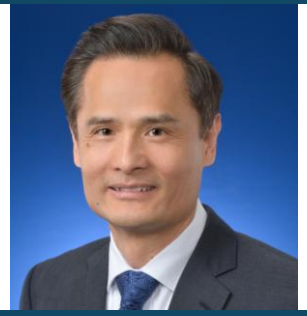


20+ years in finance, business development, and strategic operations; Ex leadership role at Alchemab, TScan, Momenta and Lilly

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

Linus Lin, PhD*



AVP of Molecular Discovery Capabilities at Lilly Global; Ex leadership role in Lilly Chorus, Lilly China R&D Center, WuXi AppTec, and Merck

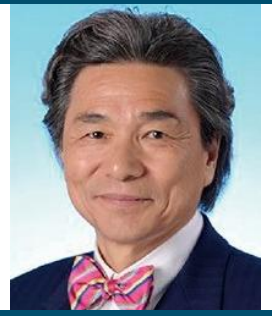
Yoshiharu Mizui, PhD*

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

Jackson Tai*

Retired board member for Lilly, HSBC Holdings, Mastercard; **Former DBS Bank CEO**, former J.P. Morgan & Co. investment banker; **Expert in finance and risk**

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**

BeyondSpring

[+]SEED Co-Founder and Scientific Advisory Board Member
*Board Member

Key Catalysts and Financing to Support RBM39 and Pipeline Growth

Strengthening RITE3™ Platform
Advancing Internal and R&D Pipelines with Lilly and Eisai

2H 2025 Catalysts:

- ST-01156 IND Cleared by US FDA
- Tau degrader in vivo efficacy

2H 2026 Catalysts:

- Phase I data for RBM39: Safety and efficacy
- Tau degrader: IND candidate expected

Financing:

- SEED raised $40 million in equity + $13 million in collaboration upfront and milestone since inception Nov. 2020;
- Series A-3 part 1 of $24 million closed ; runway to end of 2026;
- Part 2 potentially be rolled into large fundraising after our value inflection point IND is open in 2H 2025.

Summary

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 IND in 2025
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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