R&D Day Featuring Plinabulin & SEED Therapeutics

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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.

The market data and certain other statistical information used throughout this presentation are based on independent industry publications, governmental publications, reports by market research firms or other independent sources. Some data are also based on our good faith estimates. Although we believe these third-party sources are reliable, we have not independently verified the information attributed to these third-party sources and cannot guarantee its accuracy and completeness. Similarly, our estimates have not been verified by any independent source.

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

Agenda

Time (EST)	Topics	Speaker/Modulator	Affiliation
10:00 – 10:05	Introduction	Operator	ViaVid
		Shirley Liang	Finance/IR, BeyondSpring
10:05 – 10:15	Opening Remarks	Lan Huang, PhD	CEO, BeyondSpring
10:15 – 10:30	DUBLIN-3 NSCLC Phase 3 Study	Trevor Feinstein, MD	Piedmont Cancer Institute
10:30 – 10:35	Q&A		
10:35 – 10:55	Phase 1 Update on Plinabulin, Radiation and αPD-1 Triple Combo in ICI-resistant Cancers	Steven Lin, MD/PhD	MD Anderson Cancer Center
10:55 – 11:00	Q&A		
11:00 – 11:10	Unmet Need in 1L ES-SCLC	Alberto Chiappori, MD	Moffitt Cancer Center
11:10 – 11:15	Q&A		CSO/CEO, BeyondSpring
11:15 – 11:45	SEED Therapeutics	James Tonra, PhD / Lan Huang, PhD	SEED Therapeutics
11:45 – 11:50	Q&A		CSO/CEO, SEED Therapeutics
11:50 – 12:00	Closing Remarks	Lan Huang, PhD	CEO, BeyondSpring

Plinabulin Introduction

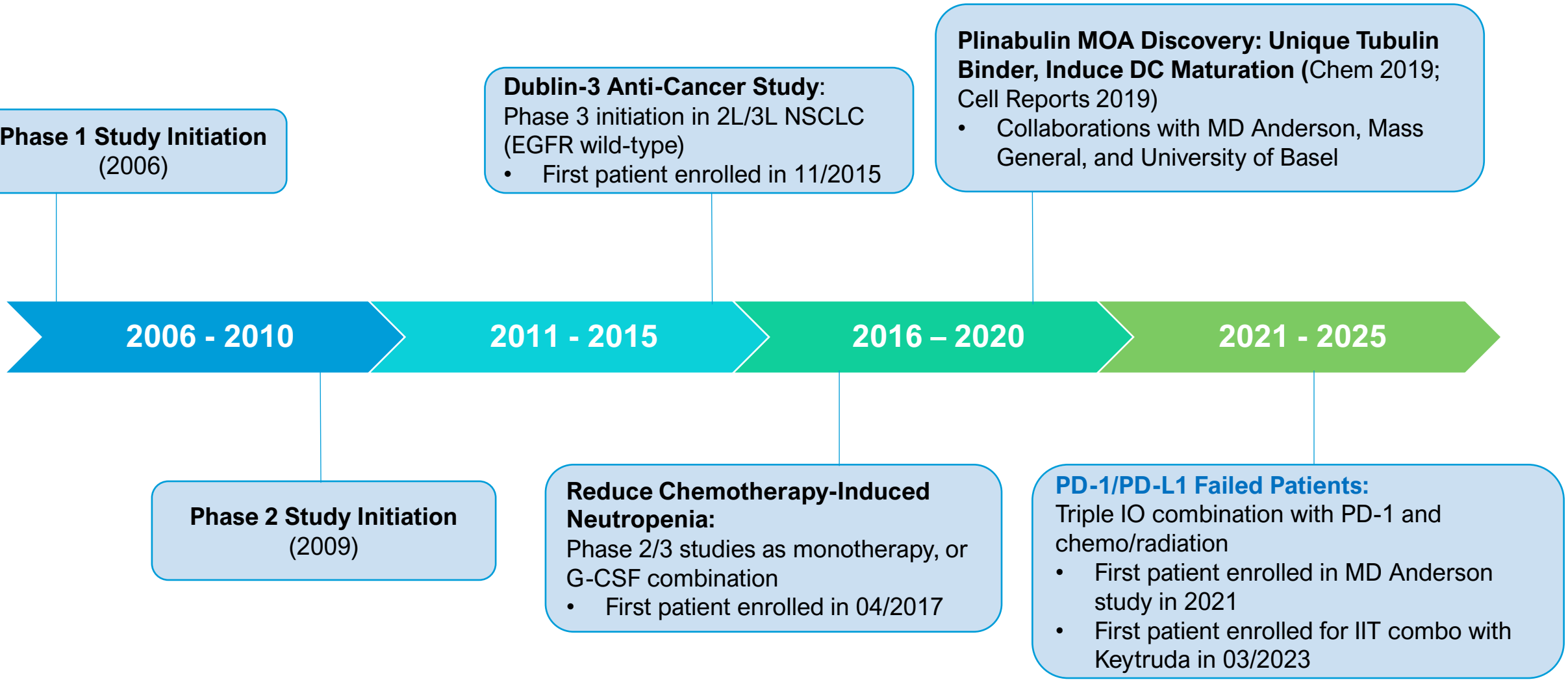
Lan Huang, PhD

BeyondSpring Pharmaceuticals, Inc.

First-in-class Lead Asset - Plinabulin

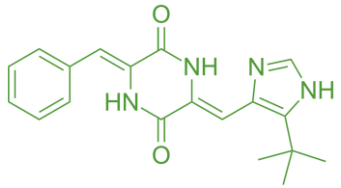
Favorable Safety Profile	**> 700 Cancer Patients** Treated with Good Tolerability
Anti-cancer Efficacy	Positive Phase 3 study in 2L/3L NSCLC with Overall Survival Benefit: 1. durable anti-cancer benefit in doubling 2-year, 3-year OS rate 2. enables more chemo doses by reducing chemotherapy-associated 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
Ease of Use	Intravenous (IV) Infusion: 1 or 2 dose per cycle
Intellectual Property	Strong Global Patent Protection: 170 granted/allowed patent to 2038 in 48 jurisdictions
Regulatory Strategy	**Multiple Phase 1/2 studies reading out in 2024 that will inform potentially pivotal randomized clinical studies beginning in 2025**

Plinabulin Development History (>700 Cancer Patients Treated)



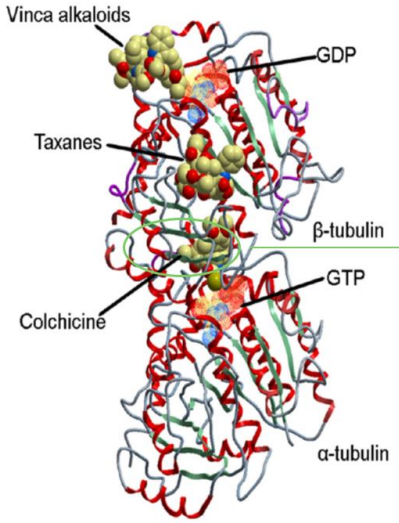
Plinabulin Drives DC Maturation and Targeted T-Cell Activation by Effectively Liberating GEF-H1 from Microtubules

Plinabulin is a unique tubulin binder[1]

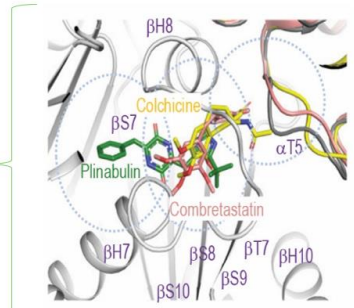


Plinabulin (NPI-2358)

Tubulin Binding Sites



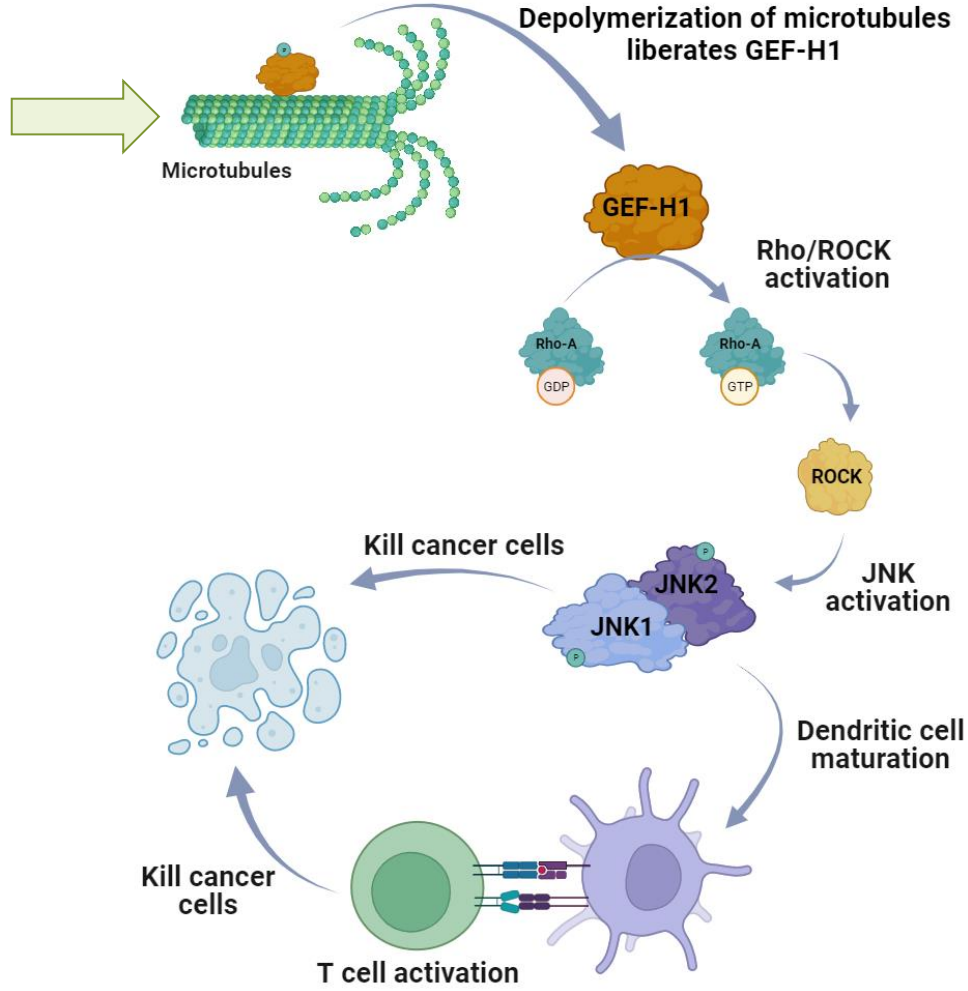
Plinabulin Binds to β-Tubulin, Near the Colchicine Site[1]



Plinabulin's tubulin binding site is distinct *from other classes of tubulin binding agents such as tubulin stabilizing taxanes (paclitaxel, docetaxel, cabazitaxel) and tubulin destabilizing vinca alkaloids (vinblastine, vincristine, vinorelbine) and colchicine.*

Plinabulin[2]

Depolymerization of microtubules

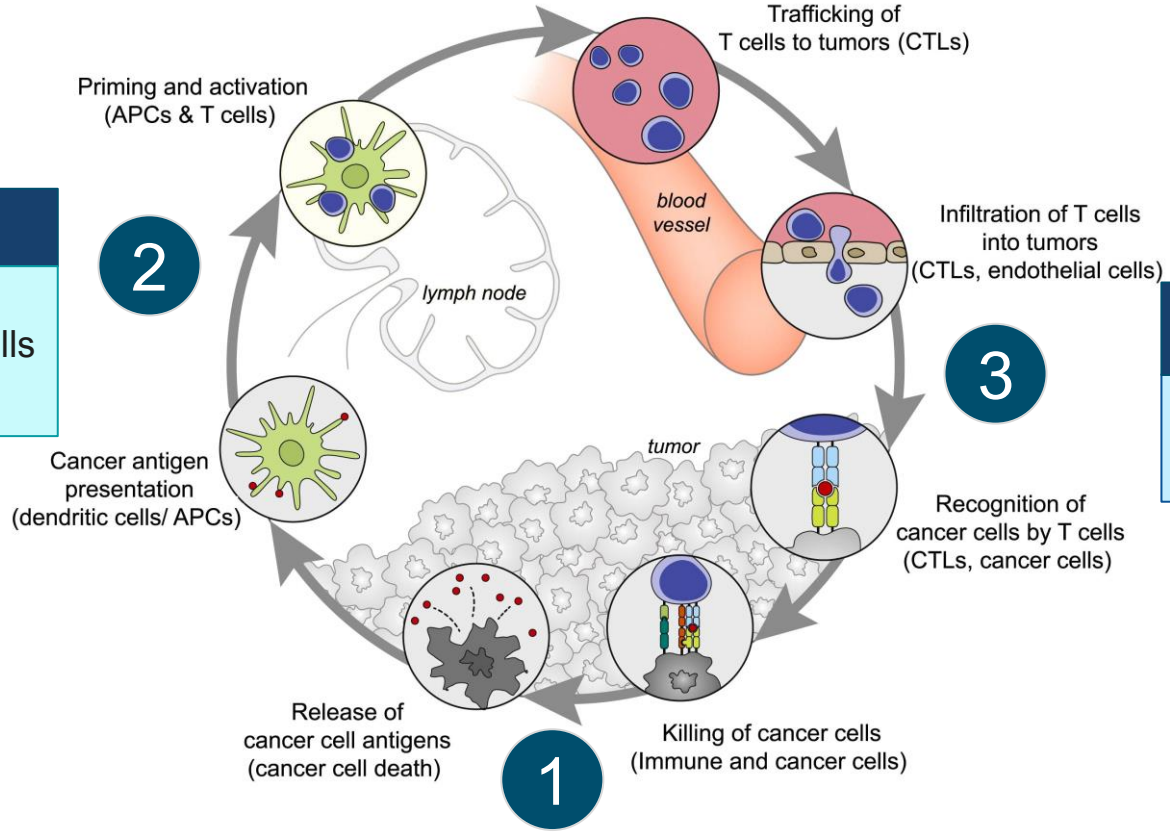


[1] La Sala et al., Chem 5(11): 2969-2986 (2019) [2] Kashyap et al., Cell Reports 28(13): 3367-3380 (2019)
GEF-H1 is a Rho guanine nucleotide exchange factor.

Plinabulin Enhances the Cancer Immunity Cycle When Used with Anti-PD-1/PD-L1 and Following Radiation or Chemotherapy

② Plinabulin

Improved antigen presentation
Stimulate maturation of dendritic cells to increase antigen presentation



③ Checkpoint Inhibitors

Anti-tumor T cell activation
Optimize T cell response

① Chemotherapy
Radiation Therapy
Oncolytic Viruses
Antibody Drug Conjugates
Targeted Therapy

① Radiation or Chemotherapy

Release tumor antigens
For more potent anti-cancer effect

Mellman I, et al. Immunity 2013; Immunity 2023

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Plinabulin as a Potential Combination Therapy with Current I/O Regimens to Address Significant Unmet Medical Needs

PD-1/PD-L1 Inhibitors
- >$40B global annual sales

→ Potential to greatly expand the addressable market

Significant Unmet Medical Needs

2L/3L: Around 60% patients fail PD-1/PD-L1 (20 cancer indications); PD-1 alone or in combo with other agents do not work

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

Plinabulin:
APC Inducer with easy administration*

Plinabulin Clinical Development

Help Re-sensitize: Plinabulin + PD-1 + chemo (IIT with Keytruda, 2L/3L NSCLC)

Enhance Anti-cancer Efficacy in durable response and reduce CIN: Plinabulin + PD-1 + chemo (IIT with Keytruda, 1L ES-SCLC)

- Acquired resistance to PD-1/PD-L1 in NSCLC is due to Antigen presentation pathway mutation or T cell exhaustion (Memon et al. Cancer Cell 42: 209-224 (2024)), which is the gap Plinabulin MOA potentially can help.
- Overtime, Plinabulin may have the potential to move into earlier lines of treatment in combination with I/O.

*Plinabulin IV Infusion: 1 dose per cycle in IIT studies

Plinabulin Clinical Development

	Indication/Target	Program	Preclinical	Phase 1	Phase 2	Phase 3	Trial Name / Collaborator	
Late stage	**NSCLC (2nd/3rd line)**	Plinabulin + Docetaxel					DUBLIN-3	✓
Late stage	**CIN Prevention**	Plinabulin alone or + Pegfilgrastim					PROTECTIVE-1 & PROTECTIVE-2	✓
Investigator-Initiated Trials	**NSCLC (2nd/3rd line PD-1 failed)**	Plinabulin + Pembrolizumab + Docetaxel					**Study 303**	**Expect Preliminary Data 2H 2024**
Investigator-Initiated Trials	**Extensive-Stage SCLC (1st line)**	Plinabulin + Pembrolizumab + Etoposide / Platinum					**Study 302**	**Expect Preliminary Data 1H 2025**
Investigator-Initiated Trials	**Multiple cancers (PD-1/PD-L1 failed)**	Plinabulin + PD-1/PD-L1 + Radiation					THE UNIVERSITY OF TEXAS MD Anderson Cancer Center	✓

Significant Unmet Medical Needs in Immune Checkpoint Inhibitor Failed Patients

Limited Options Currently Exist for Patients Who Failed PD-1/PD-L1 Inhibitors

Melanoma: Amtagvi™(lifileucel): Approved TIL cell therapy patients by Iovance Therapeutics

- > $500 K USD per dose
- Estimated annual global sales to be greater than $1 billion by 2030

Plinabulin improves overall survival and enhances safety in 2L/3L NSCLC (Dublin-3 Study)

Trevor Feinstein, MD

Piedmont Cancer Institute

Leading Expert Speaker Biography

Dr. Trevor Feinstein
Piedmont Cancer Institute

Dr. Trevor Feinstein is the recipient of numerous honors and awards, including the Thomas O'Toole Award for his outstanding work with the underserved populations; a Sanofi-Aventis Grant; and the Amgen Fellowship Award. Dr. Feinstein has authored over 50 peer-reviewed articles, abstracts and manuscripts in Hematology and Oncology. He has given international lectures on the treatment of lung cancer, including a proffered paper at ESMO (European Society for Medical Oncology) and leading the AstraZeneca Lung Cancer Summit in Beijing.

Dr. Feinstein co-runs Piedmont Cancer's research department. He sits on the Piedmont Hospital's Oncology Scientific Review Committee and is director of research at Piedmont Fayette Hospital. He is a member of Georgia CORE's research committee along with Georgia Society for Clinical Oncology Clinical Practice Committee. He also chairs the Lung Disease Group for the entire OneOncology network.

The EGFR-wild Type 2L/3L NSCLC Have Been a Historically Difficult Space in Which to Develop

Treatment options in 2L/3L NSCLC are limited

Docetaxel-based therapies are the mainstay therapy in 2L/3L NSCLC (EGFR wt).

However, **docetaxel-based therapies (SOC) demonstrate limited efficacy and are associated with >40% severe (grade 3/4) neutropenia.**

Other approved agents:

- Ramuciramab + Docetaxel vs. Docetaxel: OS HR=0.86, severe neutropenia 49% vs. 40%;
- Pemtrexed vs. Docetaxel: OS HR=0.99, severe neutropenia 5% vs. 40%.

Additionally, with immunotherapies moving to first line NSCLC, **there is a growing population of 2L/3L patients that are refractory to immunotherapy.**

Attempts to address treatment needs have been challenging

Since Nivolumab's approval 8 years ago, no new agent with a novel mechanism has been approved in this indication.

Multiple Phase 3 studies (PD-1/PD-L1 failed patients, 2L/3L NSCLC), did not meet OS endpoint vs. docetaxel:

1. SAPPHIRE: BMS' Nivolumab (PD-1 antibody) + Mirati's Sitravatinib (TKI)
2. CONTACT-01: Roche's Atezolizumab (PD-L1 antibody) + Exelixis's Cabozantinib (TKI)
3. LEAP-008: Merck's Pembrolizumab (PD-L1 antibody) + Eisai's Lenvima (TKI)
4. CANOPY-2: Novartis' Canakinumab (IL-1b antibody) + docetaxel
5. EVOKE-01: Gilead's sacituzumab govitecan-hziy (ADC - antibody drug conjugate)
6. CARMEN-LC03: Sanofi's tusamitamab ravtansine (ADC)

Recent successful phase 3 studies with mixed results:

- Lunar (TTfields vs. docetaxel): OS benefit (HR=0.74), but no PFS and ORR benefit;
- TROPION-Lung01 (Datopotamab deruxtecan - ADC vs. docetaxel): OS benefit (HR=0.90) in ITT population, with better OS (HR=0.75) in non-squamous NSCLC.

Plinabulin Has Been Evaluated in Combination with Docetaxel in a Phase 3 Study with 2L/3L advanced and Metastatic NSCLC 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

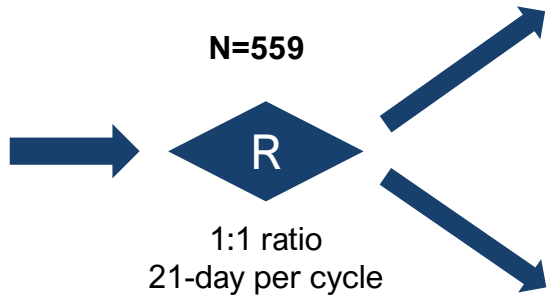
Overall survival (OS)

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)

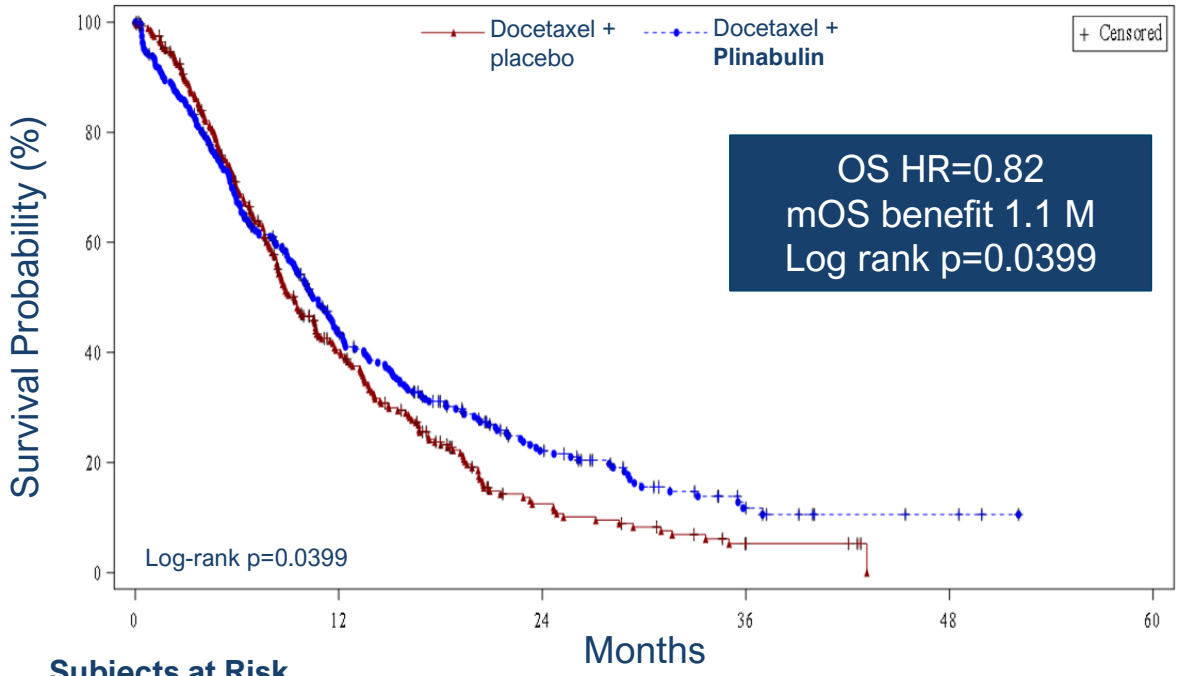
[1] 85% CPI naïve; **15% failed PD-(L)1 blockade**

Baseline and Disease 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	11 (3·9)	9 (3·2)
Missing	1 (0·4)	0 (0·0)
Regional distribution, n (%)		
Asian	245 (87·2)	243 (87·4)
Western	36 (12·8)	35 (12·6)

	Docetaxel + Placebo n=281	Docetaxel + Plinabulin n=278
Median age, y (range)	60 (25, 85)	61 (37, 82)
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)
Previous radiotherapy, n (%)		
Yes	84 (29·9)	87 (31·3)
No	197 (70·1)	191 (68·7)
Previous surgery, n (%)		
Yes	138 (49·1)	123 (44·2)
No	143 (50·9)	155 (55·8)

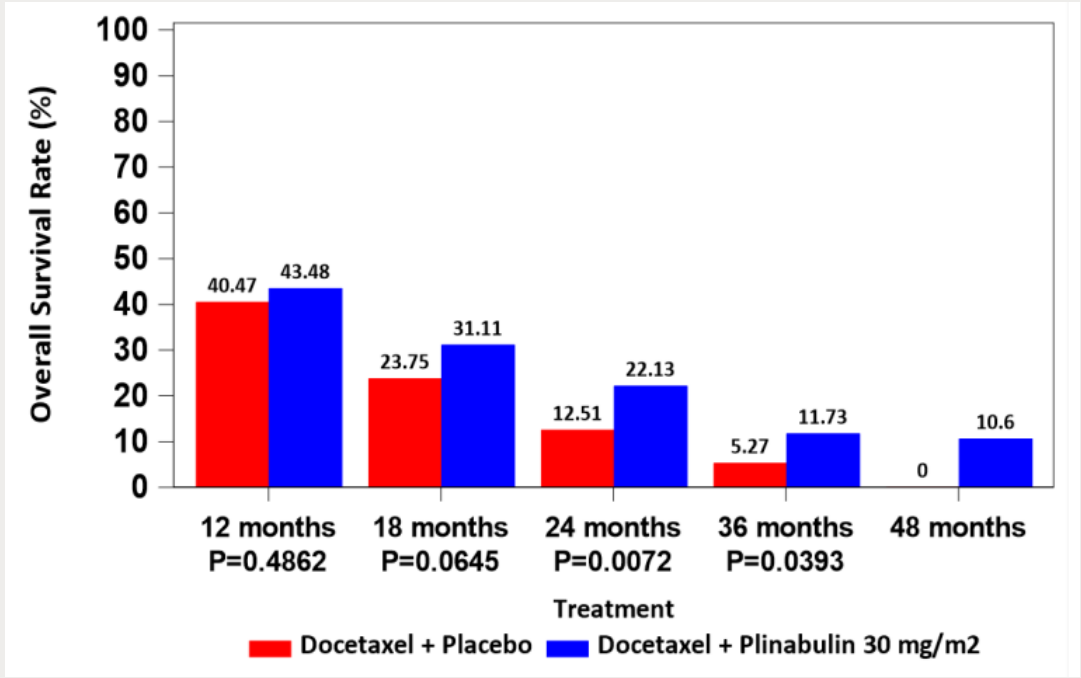
Plinabulin + Docetaxel Met its Primary Endpoint (OS) and Showed Significant Improvement in Long-term OS Rate



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)

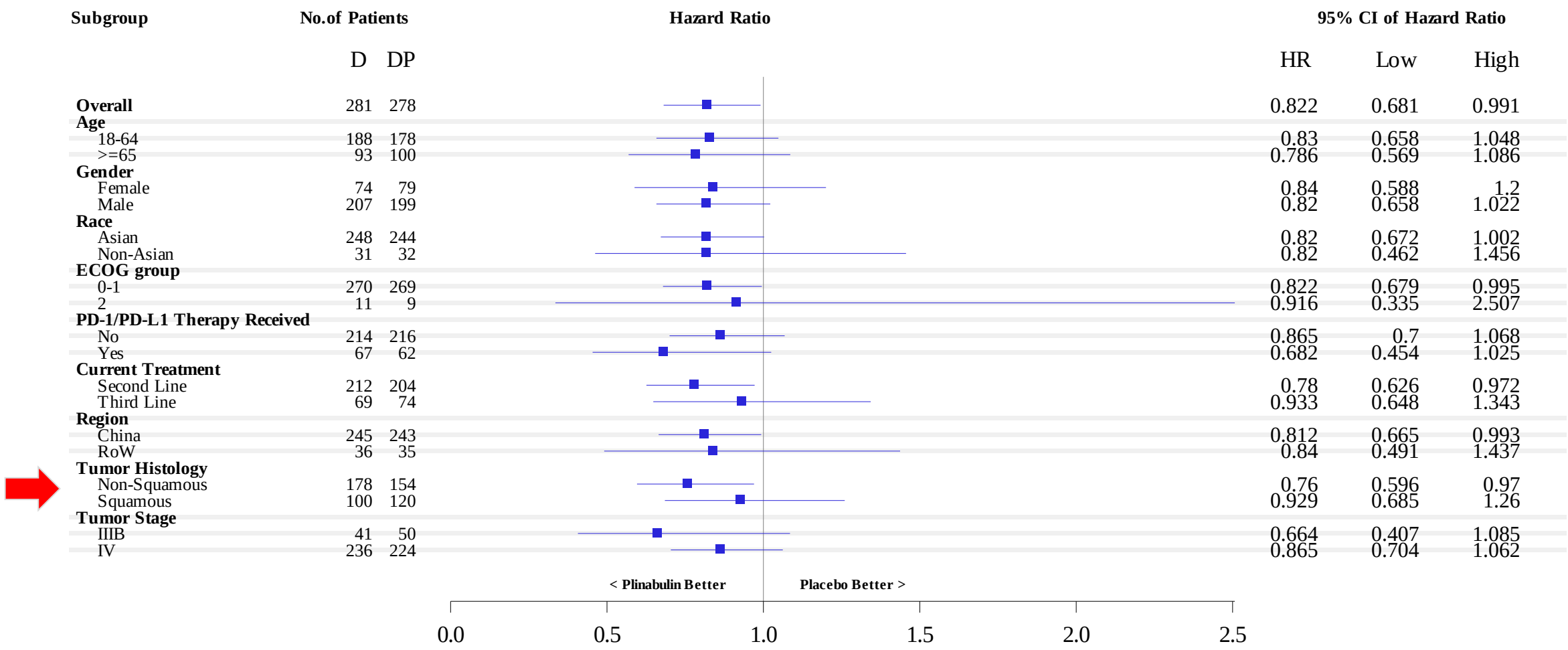


OS Rate Increase Results

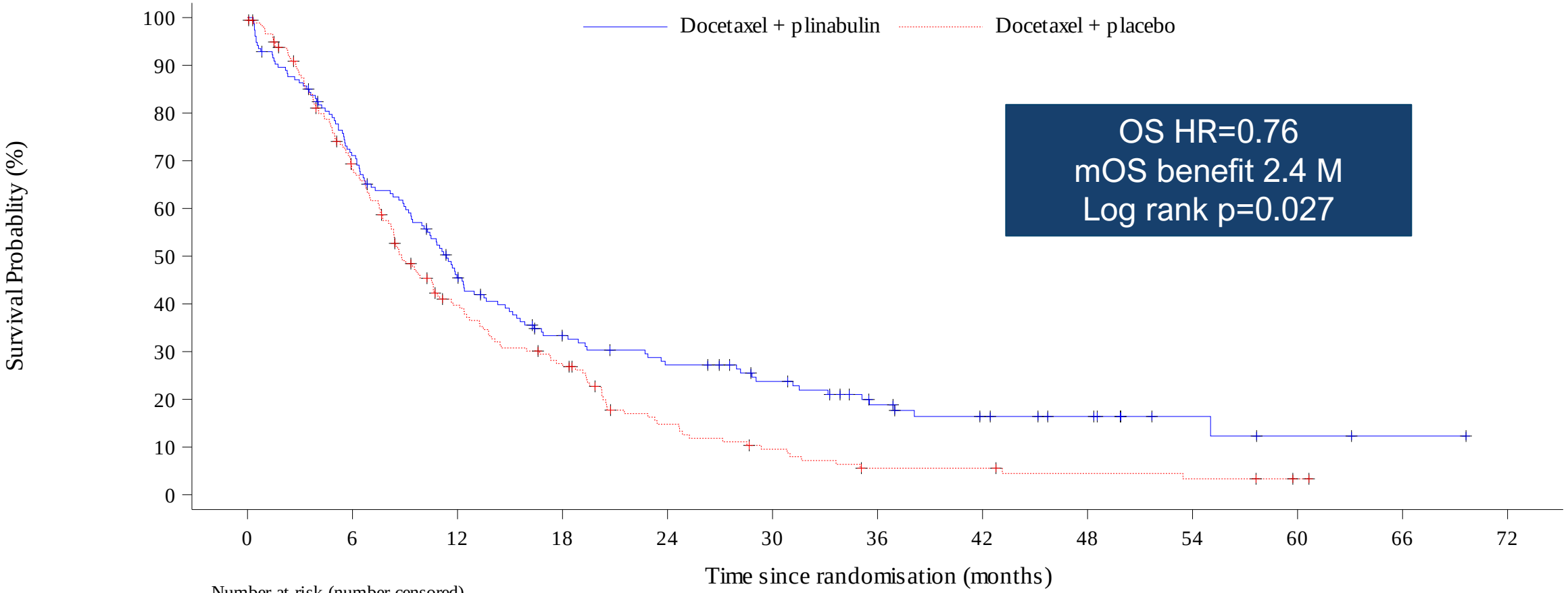
- Significantly increased OS rate in 24 months, and 36 months (doubling benefit)
- 48m OS rate: D + Product X (10.6%) vs D (0%)

OS Forest Plot - Global ITT Population

HR<1: Better Efficacy in DP Arm



Subset Analysis: Significant Survival Benefit in Non-squamous NSCLC



Number at risk (number censored)

Docetaxel + plinabulin	154(0)	107(3)	66(6)	44(11)	35(12)	27(16)	17(21)	12(24)	9(27)	4(32)	2(33)	1(34)	0(35)
Docetaxel + placebo	178(0)	115(8)	62(14)	42(15)	20(19)	12(20)	6(21)	6(21)	4(22)	3(22)	1(24)	0(25)	

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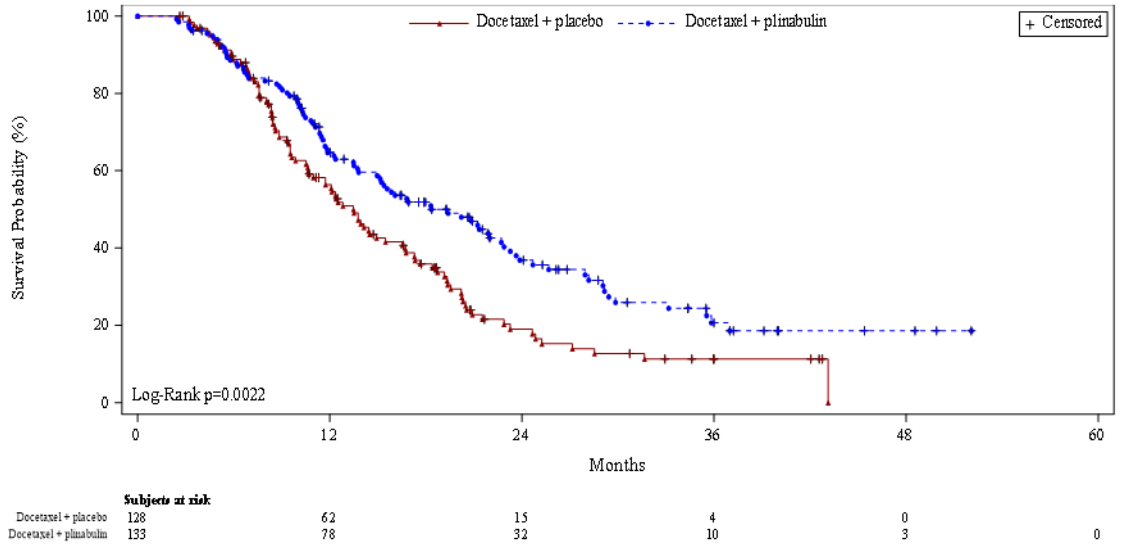
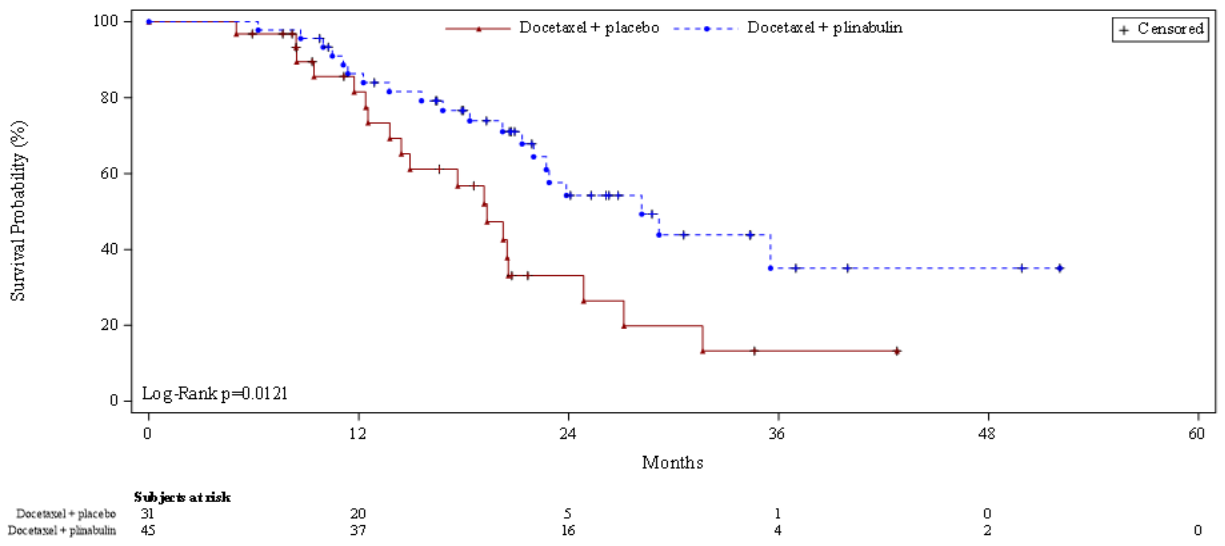
Improved OS Benefit in Patients with More Cycles of Treatment

OS K-M Graph for treatment cycles >= 4 cycles



	Median OS	p value
D (n= 128)	13.5(10.68,16.54)	
DP (n= 133)	18.3(14.96,22.88)	HR=0.634; P = 0.0022

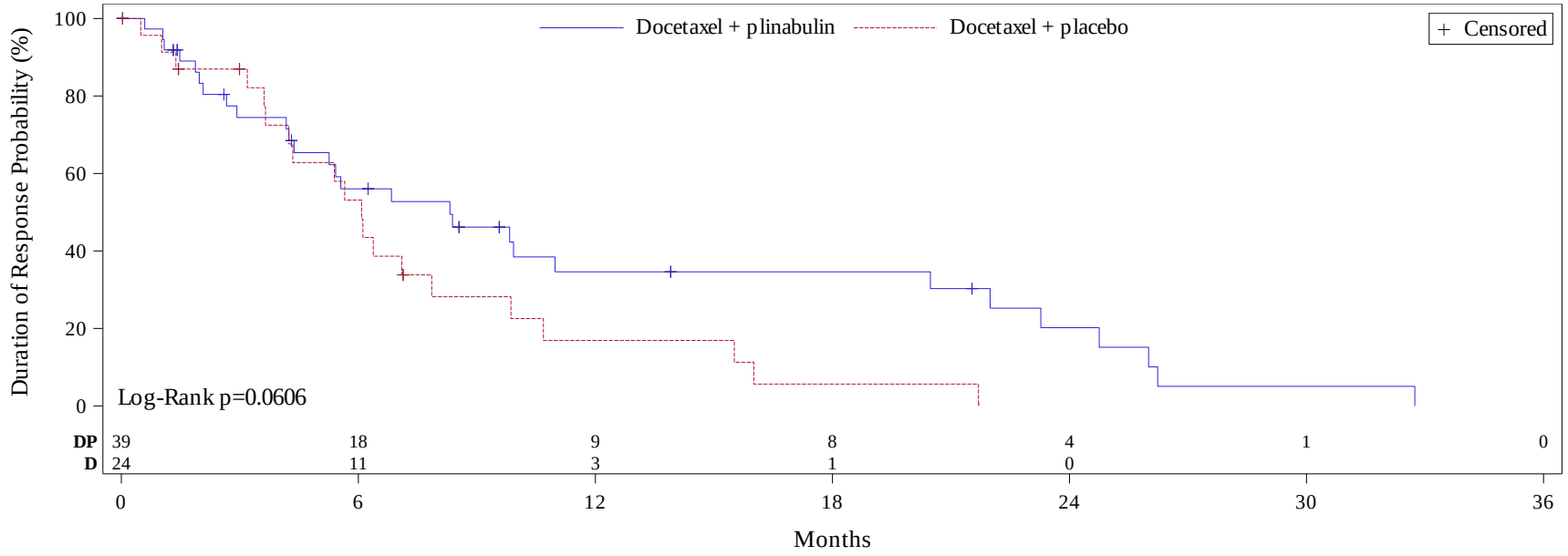
OS K-M Graph for treatment cycles >= 8 cycles



	Median OS	p value
D (n= 31)	19.3(13.77,24.85)	
DP (n= 45)	28.2(21.99,NA)	HR=0.453; P = 0.0121

Improved Duration of Response (DOR*)

Durable Anti-cancer Benefit



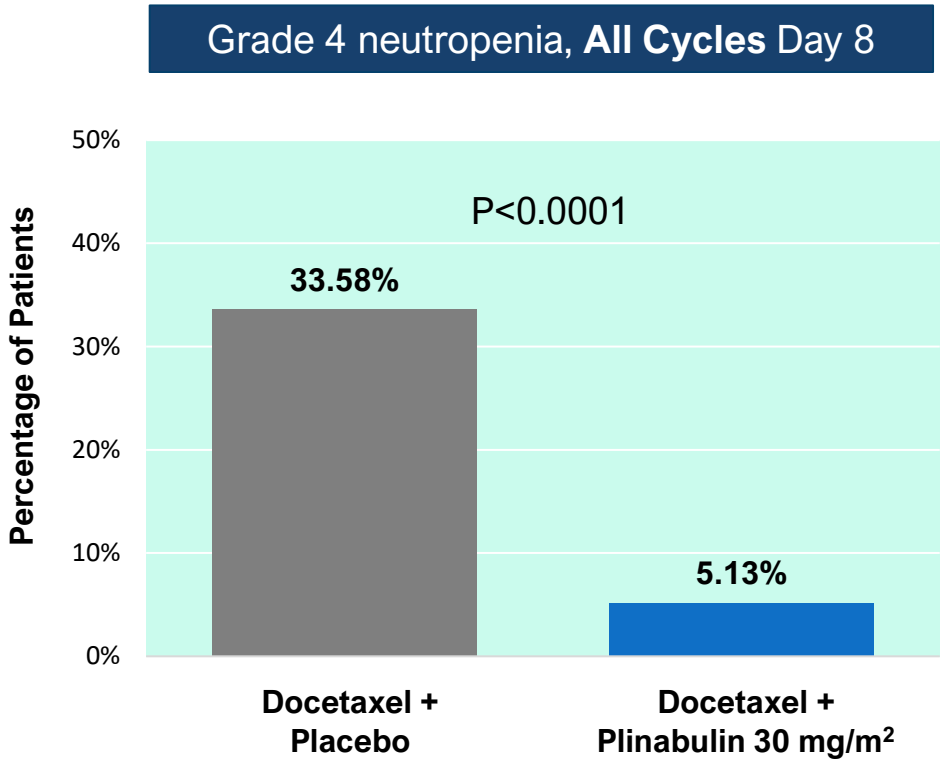
Treatment	Subjects	Event	Censored	Median (95% CI)	HR (95% CI)
Docetaxel + placebo	24	20 (83.3%)	4 (16.7%)	6.08 (3.65,7.86)	
Docetaxel + plinabulin	39	28 (71.8%)	11 (28.2%)	8.32 (4.37,20.48)	0.559(0.302,1.034)

DOR	Docetaxel (75 mg/m2) N=24	Plinabulin (30 mg/m2) + Docetaxel (75 mg/m2) N=39
Median Months (95% CI)	**6.08 (3.65, 7.86)**	**8.32 (4.37, 20.48), p=0.06**

*Central Lab Radiology

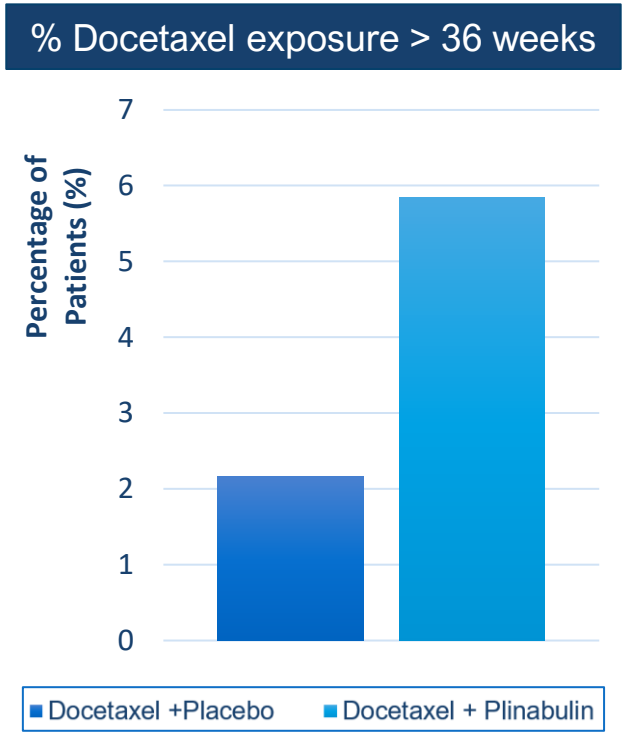
Plinabulin Not Only Slows Progressive disease, but Also Increased the Tolerability of Docetaxel and Increased Duration of Treatment

Use of plinabulin significantly reduced Grade 4 neutropenia



Similar results were observed for Grade 4 neutropenia on Cycle 1 Day 8

…allowing more patients to remain on docetaxel for a longer duration

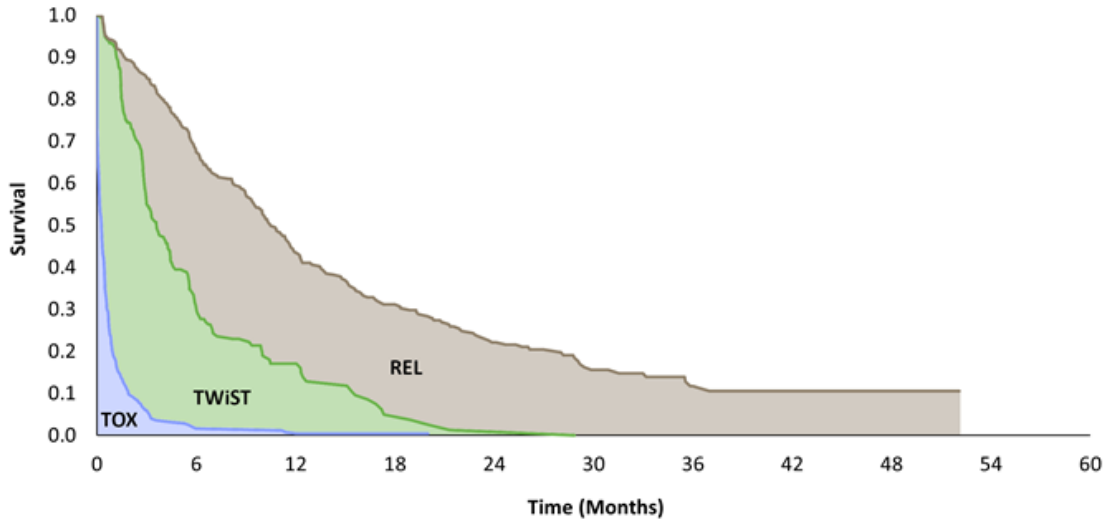


Addition of plinabulin to docetaxel also increased docetaxel exposure by mean dose (mg)

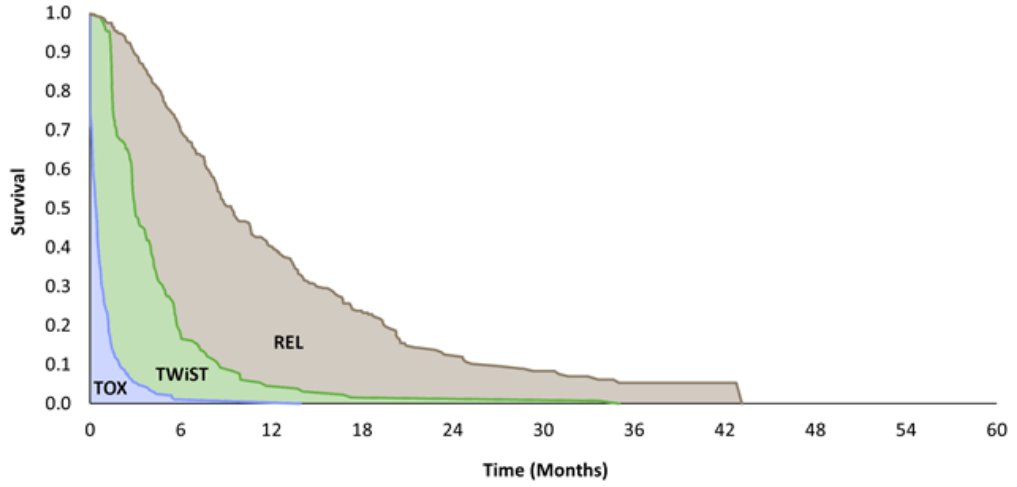
Significant Improvement in Quality-of-Life Benefit in DP vs. D

Q-TWiST (Quality-Adjusted Time Without Symptoms of Disease and Toxicity)

Plinabulin + Docetaxel



Egret alone



Q-TWiST Gain	Relative Gain to OS Restricted Mean	Relative Gain to Q-TWiST
1.93	15.11%	18.43%
	(1.72% to 30.63%)	(2.07% to 37.20%)
	p-value=0.0396	p-value=0.0393

Clinically Meaningful Improvement of >18% in Q-TWiST.

Q-TWiST benefit in DP vs D (18.4%) is comparable to that of Keytruda vs. D (20%) in Keynote-010 study[1].

1. Huang M et al. *PharmacoEconomics* **2019**; 37: 105.

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)
Haematological						
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						
Diarrhoea	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
Dyspnoea	47 (16·9)	6 (2·2)	6 (2·2)	38 (13·9)	5 (1·8)	1 (0·4)
Haemoptysis	27 (9·7)	1 (0·4)	0	31 (11·3)	4 (1·5)	1 (0·4)

Plinabulin Successfully Improved Efficacy of SOC in 2L/3L NSCLC (EGFR WT), Proving its Clinical Utility

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

Efficacy

- Significant survival benefit in ITT (OS HR=0.82)
- Even more pronounced survival benefit in 2L (HR=0.78), or non-squamous NSCLC (HR=0.76)

Safety and tolerability

- The regimen is generally well tolerated
- Side effects include transient hypertension that resolves in 4-6 hours, nausea, vomiting and GI side effects, which can be managed with prophylactic anti-emetic therapy
- Significant QoL benefit
- Docetaxel-induced neutropenia was **significantly** reduced, allowing increased treatment exposure

BeyondSpring

BeyondSpring

Preclinical and Clinical POC immunomodulating activity of Plinabulin inducing Dendritic Cell maturation and Re-sensitization in Immunotherapy Refractory Tumors when Combined with Radiation and PD-1/PD-L1 Inhibitors

Steven Lin, MD, PhD

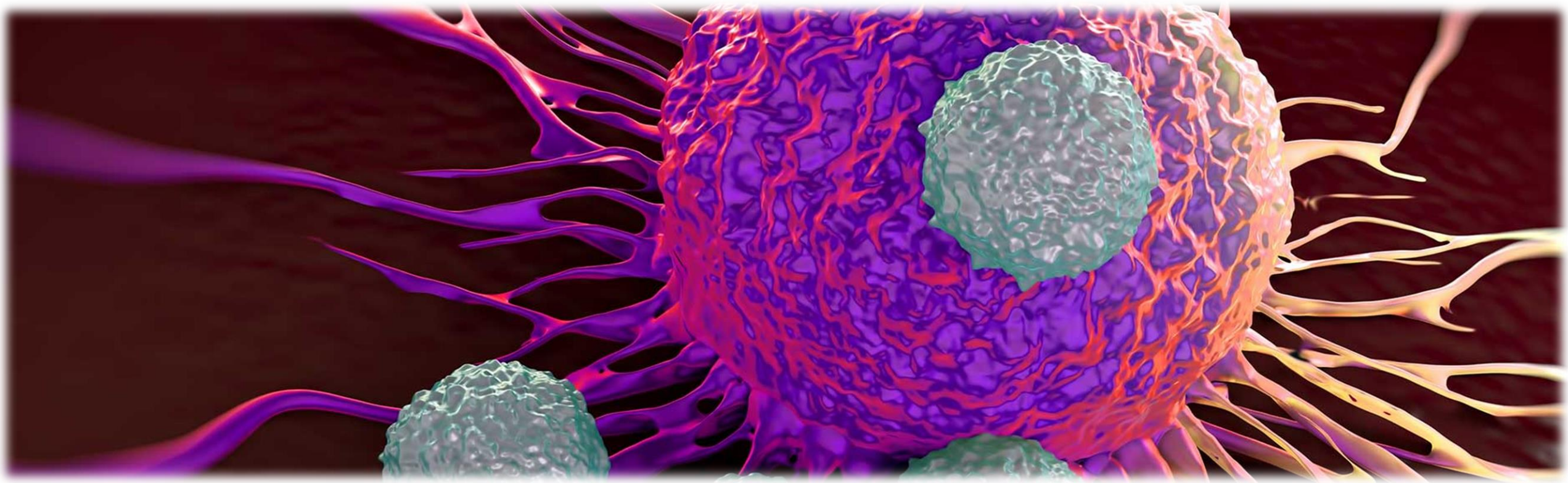
MD Anderson Cancer Center

Leading Expert Speaker Biography

Dr. Steven Lin, MD Anderson Cancer Center

Dr. Steven Lin is a Professor and Physician Scientist, with joint appointments in the Departments of Radiation Oncology and Experimental Radiation Oncology. Dr. Lin's practice focuses on thoracic malignancies, and he oversees several clinical trials including the use of proton beam therapy for esophageal cancer and in the combination of immunotherapy with radiotherapy in lung and esophageal cancers.

Dr. Lin runs a translational research team that evaluates biomarkers for treatment response and disease outcomes after chemoradiation therapy and immunotherapy. On the basic science side, Dr. Lin's main interests lie in identifying novel approaches that could enhance radiotherapy and immunotherapy combinations in lung cancer that could be translated to innovative clinical trials for patients.

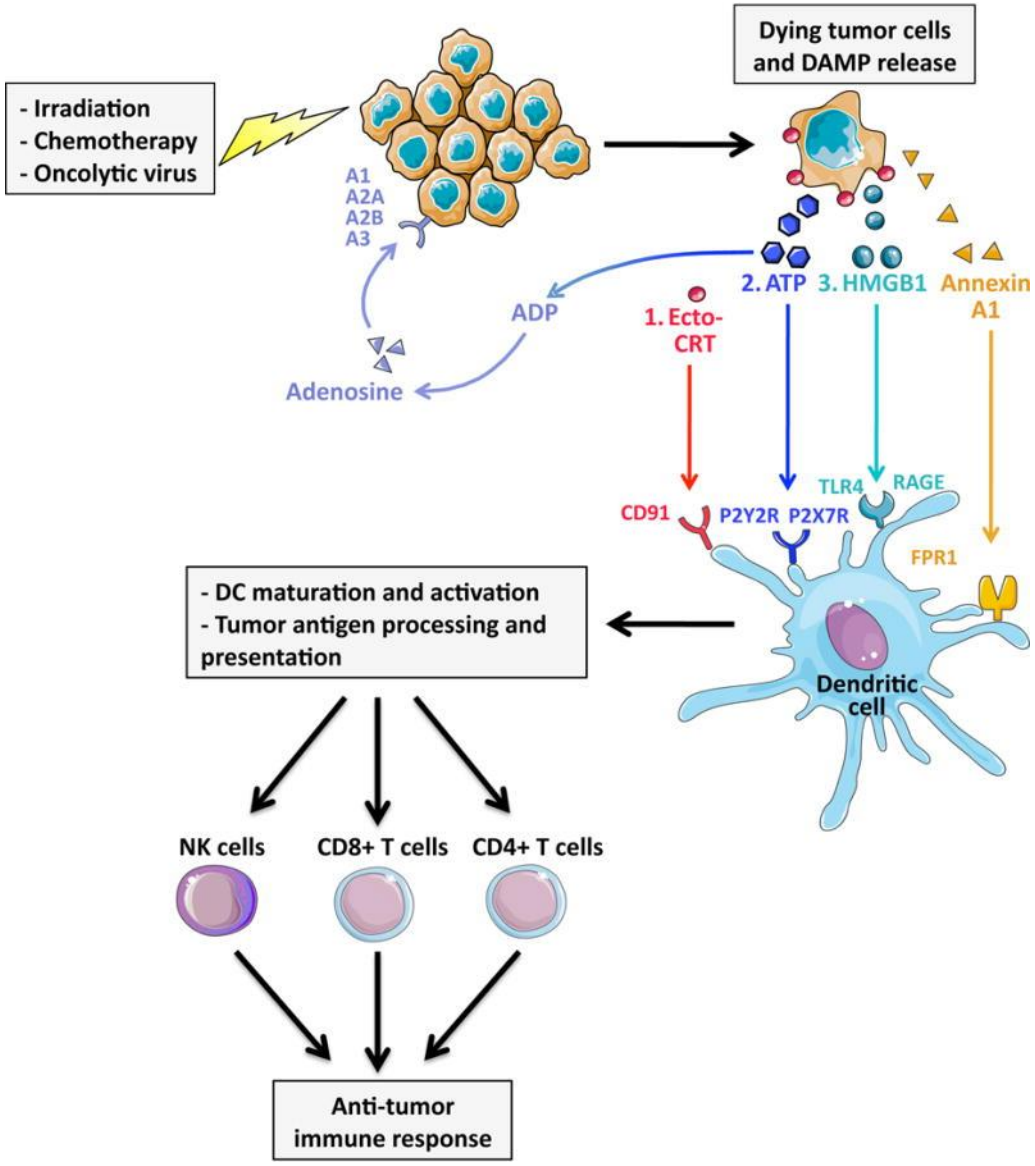


THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Anti-cancer Immunity using Plinabulin in Combination with Radiation and Immune Checkpoint Inhibitors

Steven H. Lin, MD, PhD
Professor
Thoracic Radiation Oncology

Radiotherapy could stimulate an immune response through activating dendritic cells



Hernandez C et al., Oncogene 2016

Does radiotherapy induce anti-cancer immune response with immune checkpoint blockade? Promising in early-stage disease

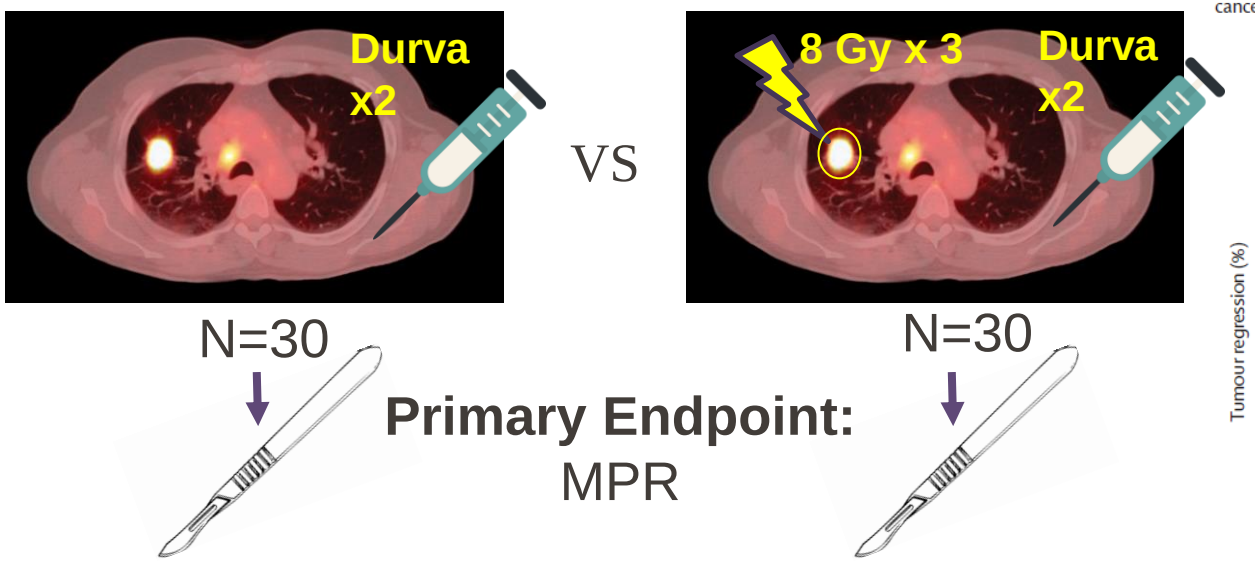
Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial

Nasser K Altorki, Timothy E McGraw, Alain C Borczuk, Ashish Saxena, Jeffrey L Port, Brendon M Stiles, Benjamin E Lee, Nicholas J Sanfilippo, Ronald J Scheff, Bradley B Pua, James F Gruden, Paul J Christos, Cathy Spinelli, Joyce Gakuria, Manik Uppal, Bhavneet Binder, Olivier Elemento, Karla V Ballman, Silvia C Formenti

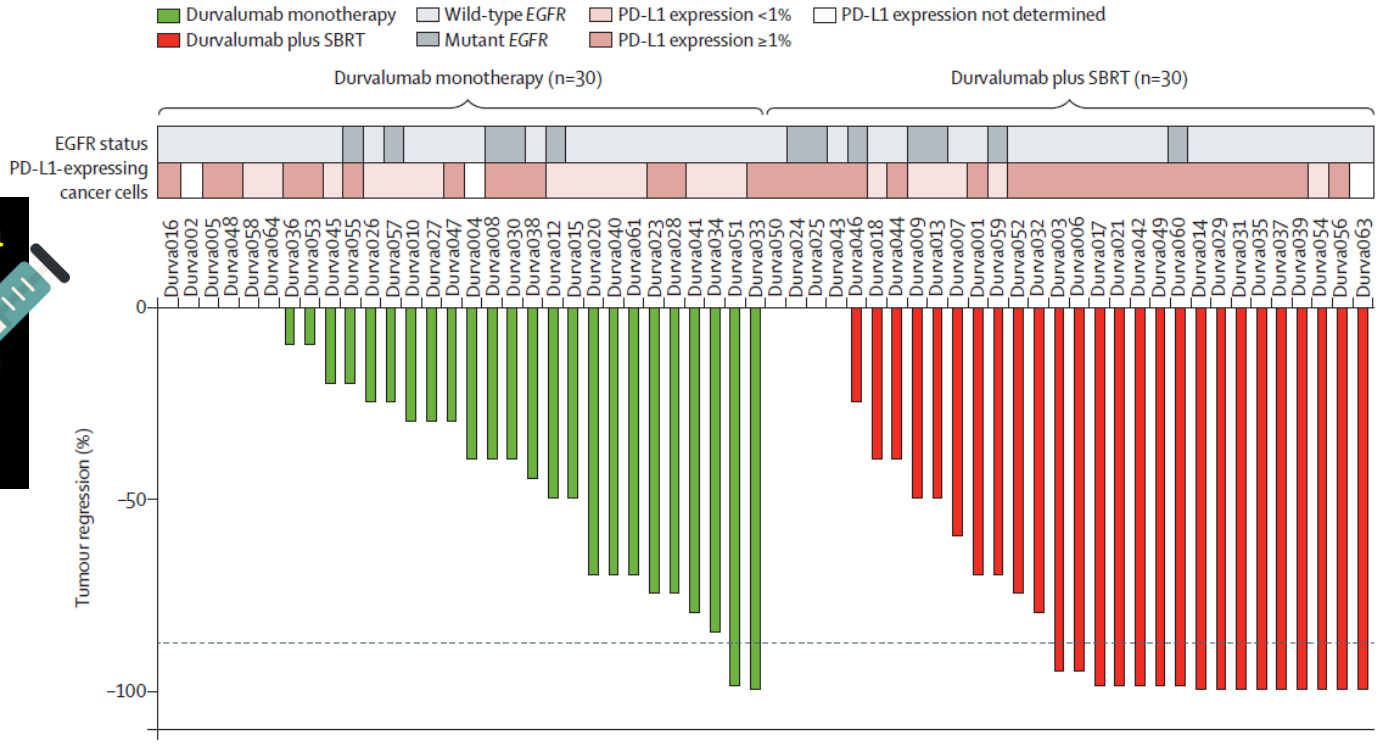
Durva alone
- MPR = 6%
- PCR = 0%

Durva + SBRT
- MPR = 53%
- PCR = 27%

Stage I-IIIA **resectable** NSCLC (before Checkmate 816)



Primary Endpoint:
MPR



Altorki et al., Lancet Oncol 2021

Phase II RCT of Durva/Treme +/- RT in PD-1 refractory advanced NSCLC (negative trial)

Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non-small-cell lung cancer refractory to previous PD(L)-1 therapy: an open-label, multicentre, randomised, phase 2 trial

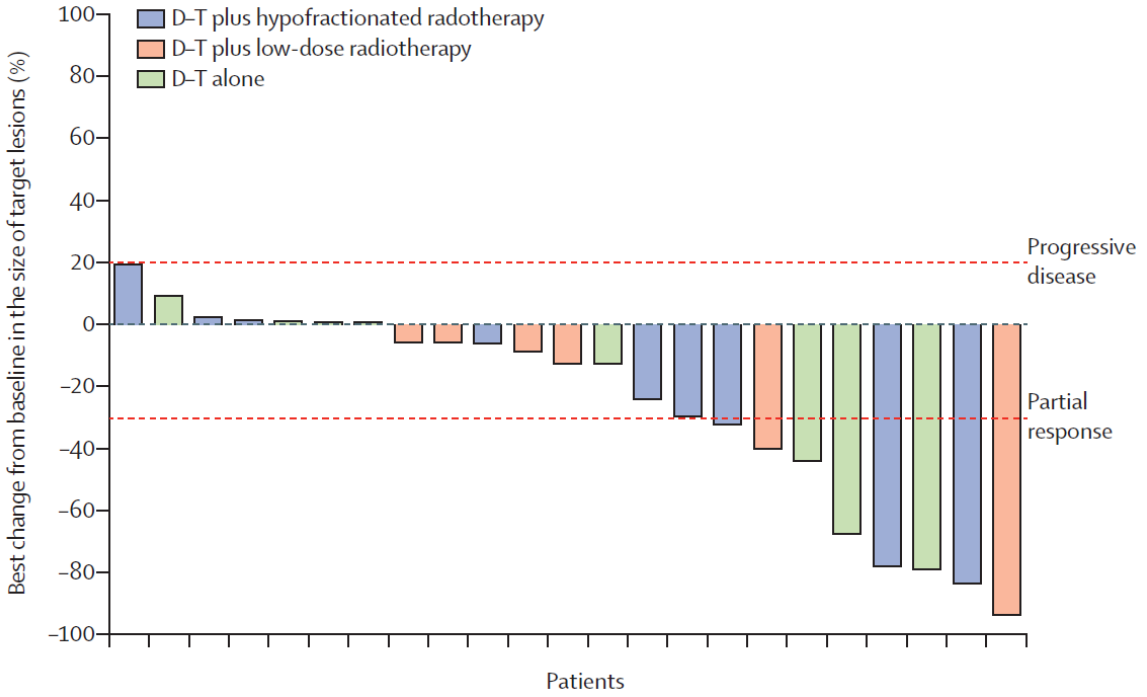
Jonathan D Schoenfeld, Anita Giobbie-Hurder, Srinika Ranasinghe, Katrina Z Kao, Ana Lako, Junko Tsuji, Yang Liu, Ryan C Brennick, Ryan D Gentzler, Carrie Lee, Joleen Hubbard, Susanne M Arnold, James L Abbruzzese, Salma K Jabbour, Nataliya V Uboha, Kevin L Stephans, Jennifer M Johnson, Haeseong Park, Liza C Villaruz, Elad Sharon, Howard Streicher, Mansoor M Ahmed, Hayley Lyon, Carrie Cibuskis, Niall Lennon, Aashna Jhaveri, Lin Yang, Jennifer Altreuter, Lauren Gunasti, Jason L Weirather, Raymond H Mak, Mark M Awad, Scott J Rodig, Helen X Chen, Catherine J Wu*, Arta M Monjazeb*, F Stephen Hodi**

- Overall Response (CR+PR) = **10%**
- Disease control rate (CR/PR/SD) = **30%**

Radiotherapy:

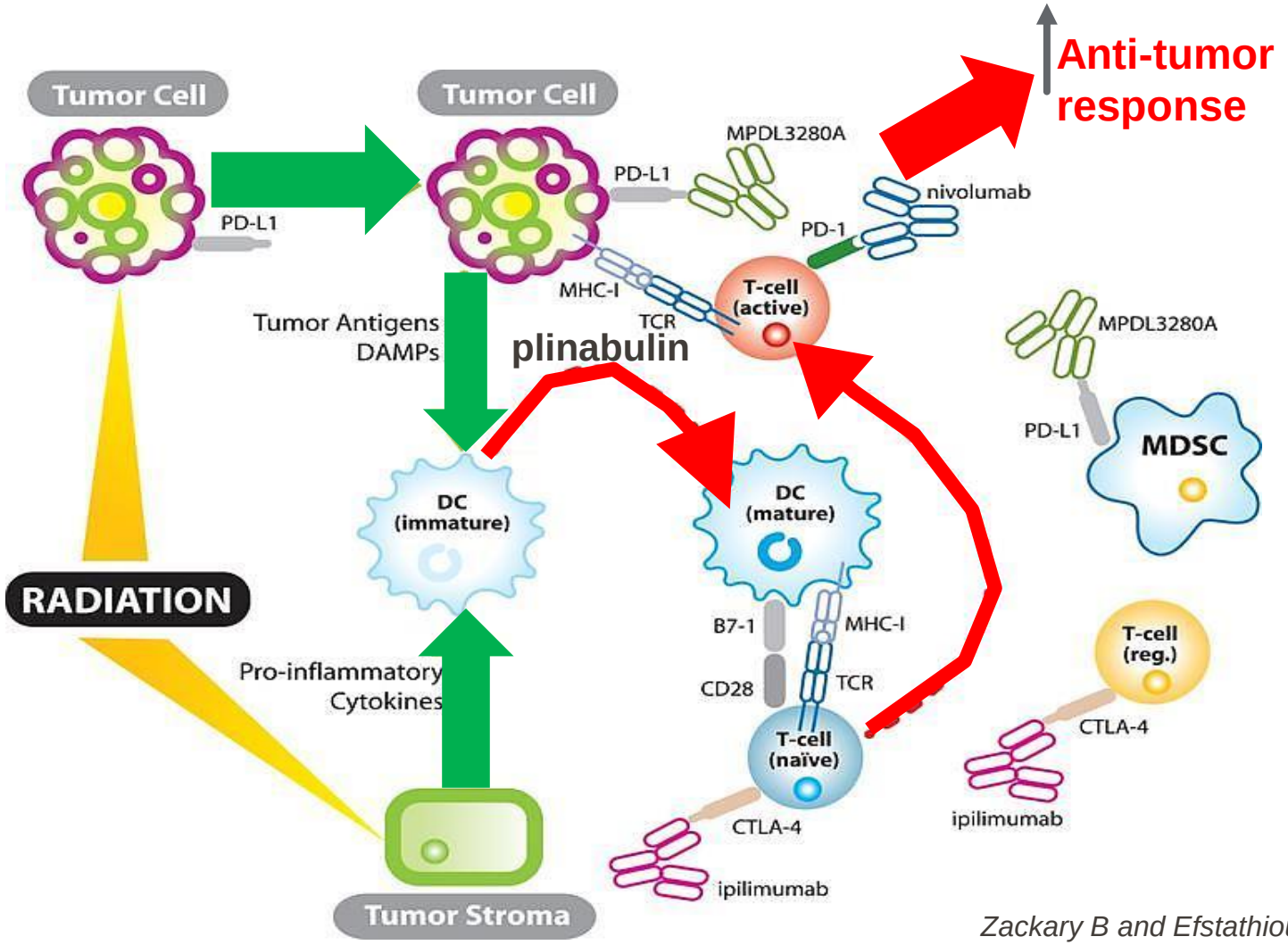
Low dose: 0.5 Gy BID QOD x 4 wks = 8 Gy

Hypofx RT: 8 Gy x 3 (one week) = 24 Gy



Schoenfeld et al., Lancet Oncol 2022

Can we augment the effect of radiotherapy in combination with immunotherapy? Yes, by further Activating Dendritic Cells

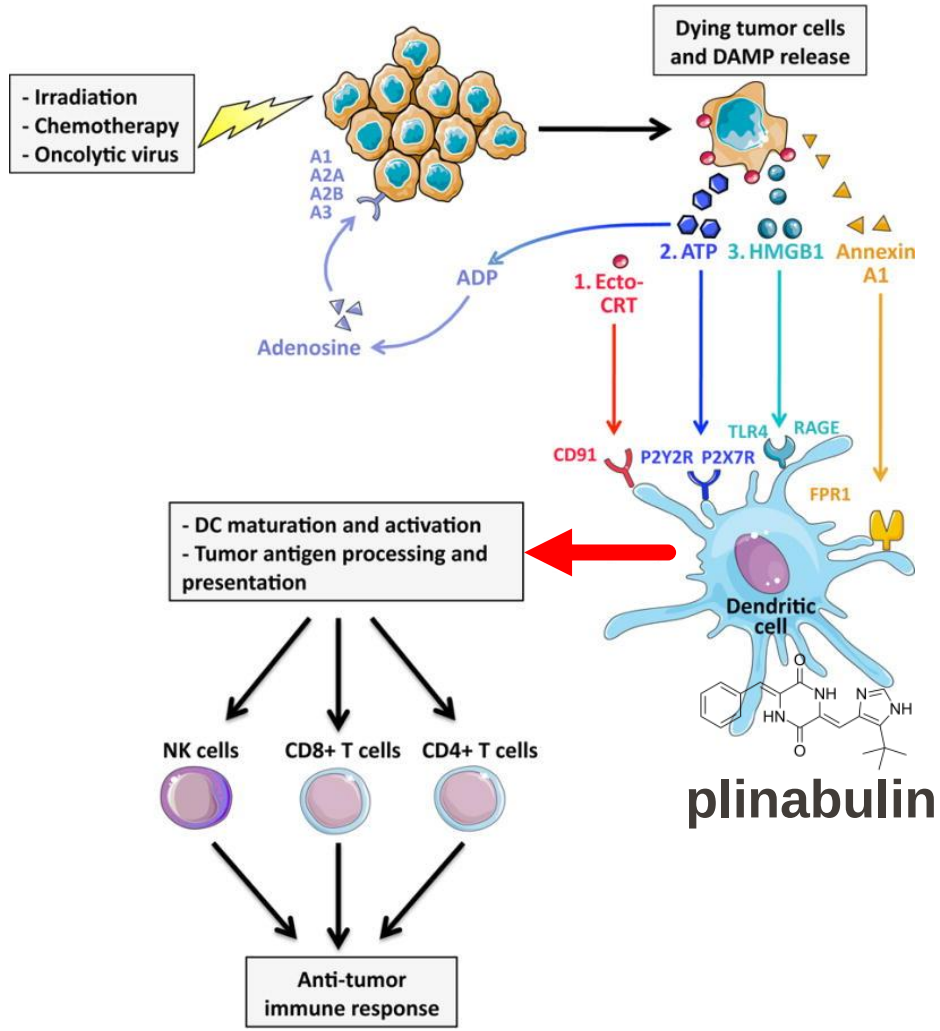


Zackary B and Efstathiou J, Bladder Cancer 2015

Hypothesis for the Phase I MDACC trial

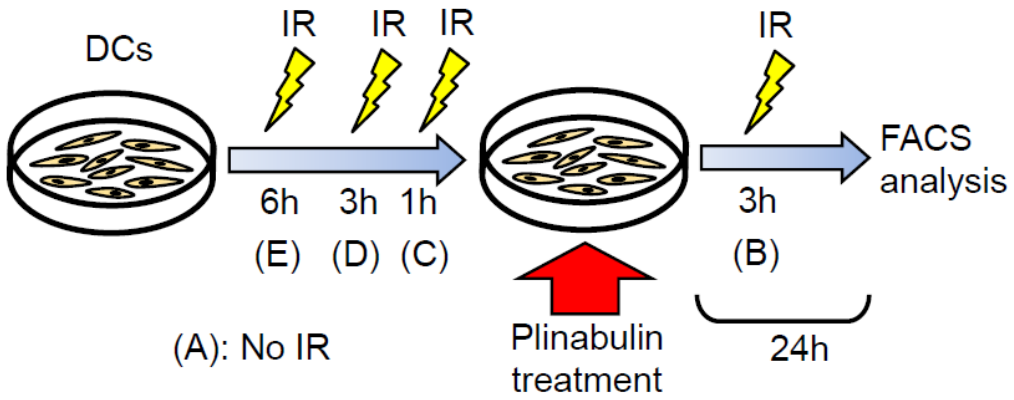
Priming the system with radiation followed by plinabulin + anti-PD-L1 is safe and efficacious in immunotherapy progressing advanced malignancies

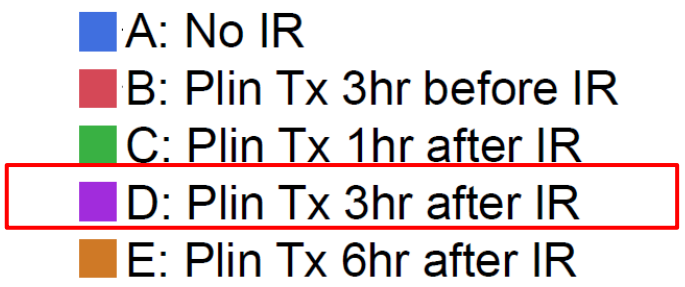
- **Need preclinical evidence to demonstrate RT priming followed by plinabulin could elicit anti-tumor immune response**

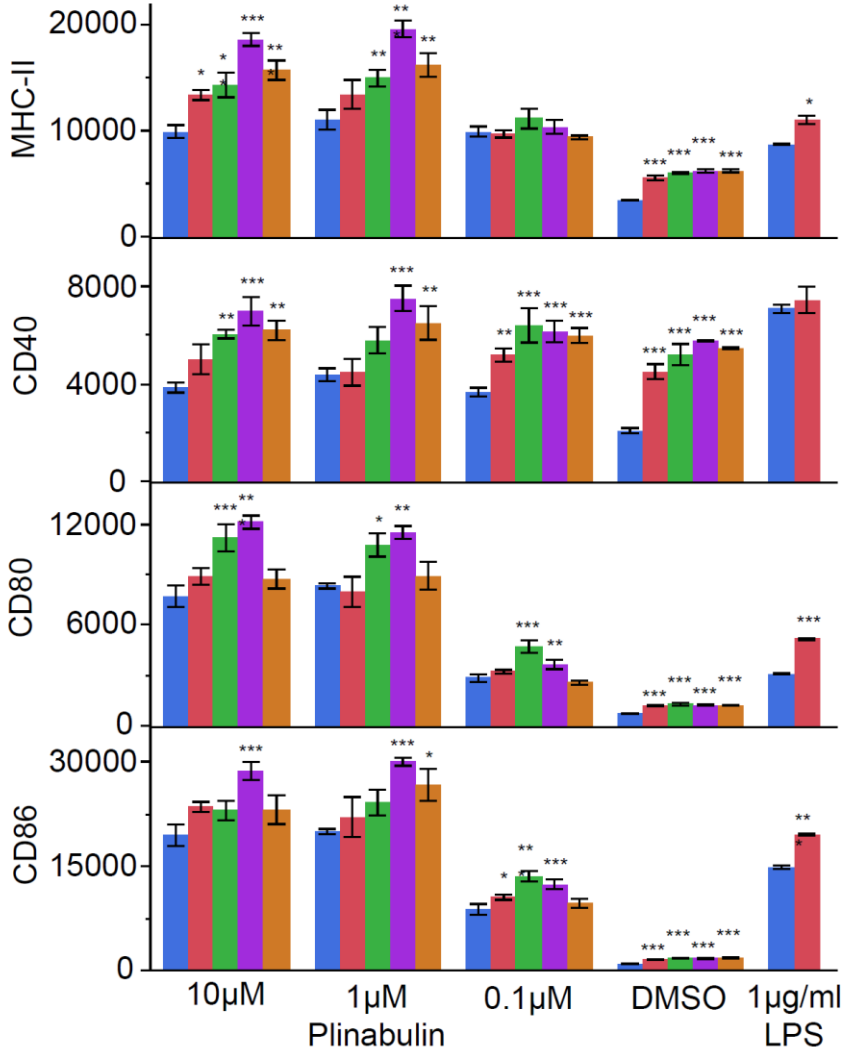


Hernandez C et al., Oncogene 2016

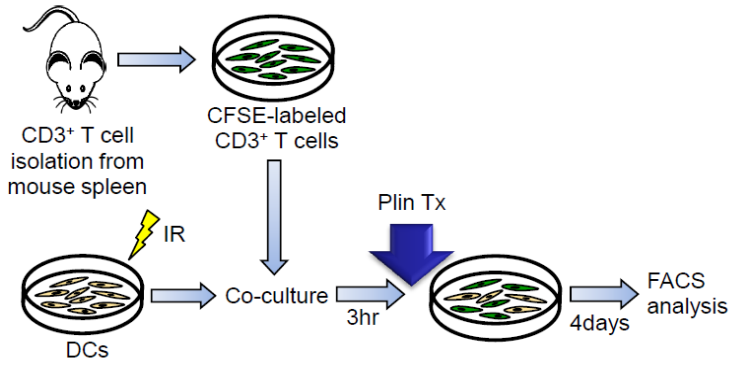
Optimal Sequencing of IR with Plinabulin to elicit DC activation: RT before plinabulin (3 hrs) but not Plinabulin before RT

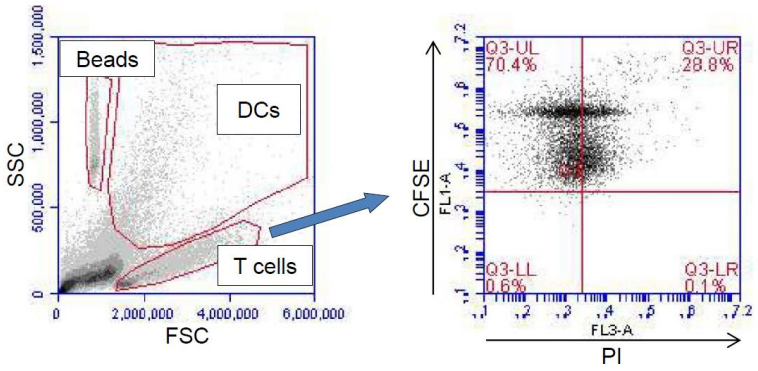


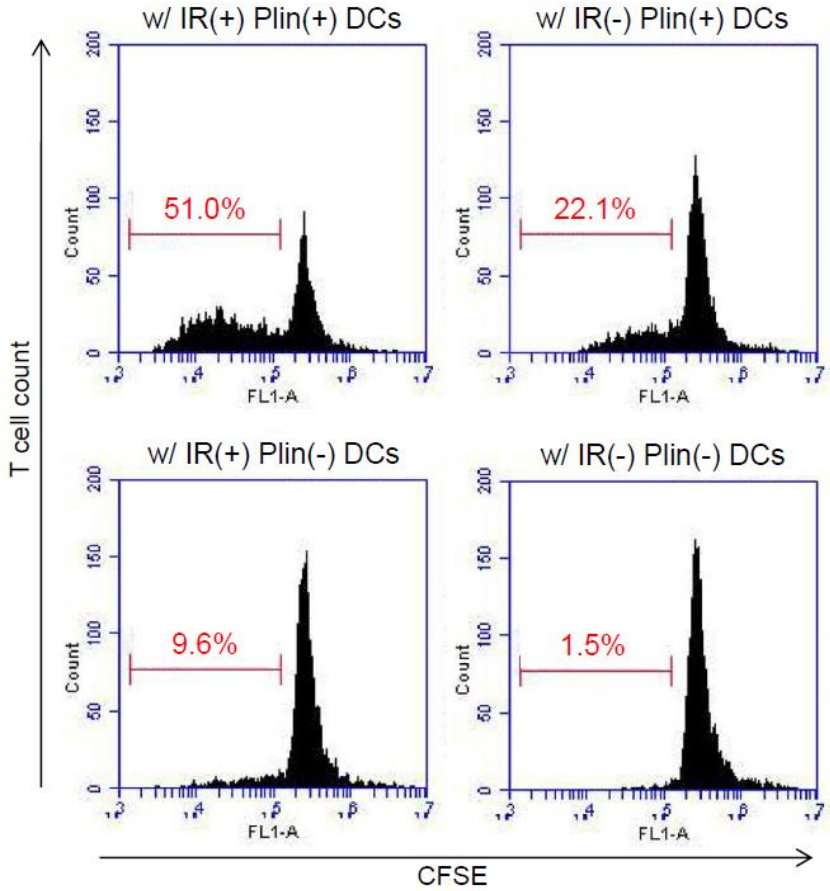


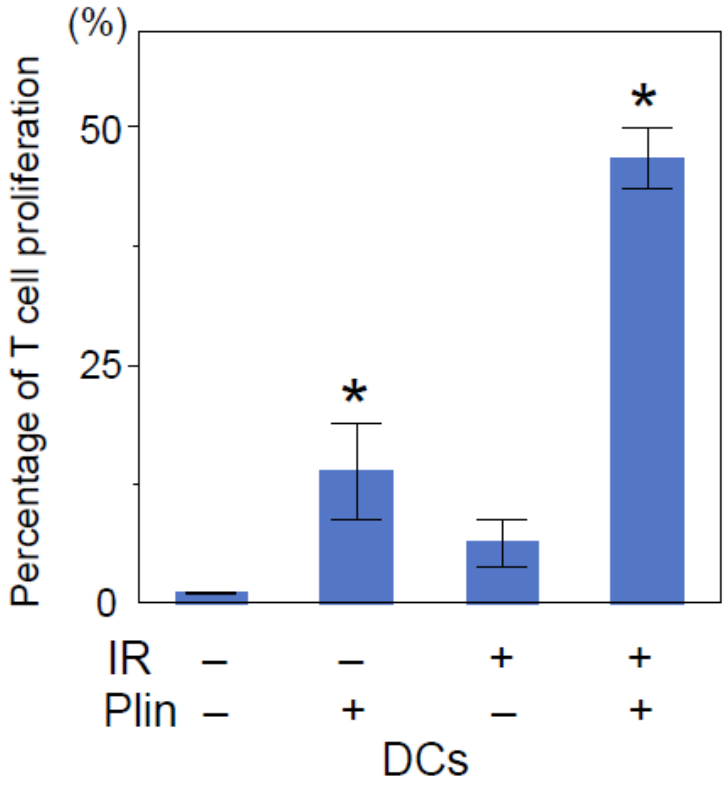


Plinabulin + RT enhances T-cell proliferation in mixed lymphocyte reaction

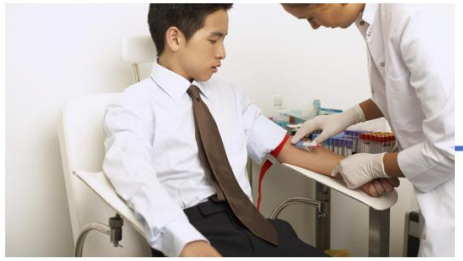


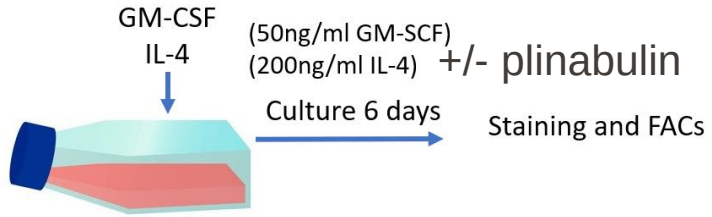




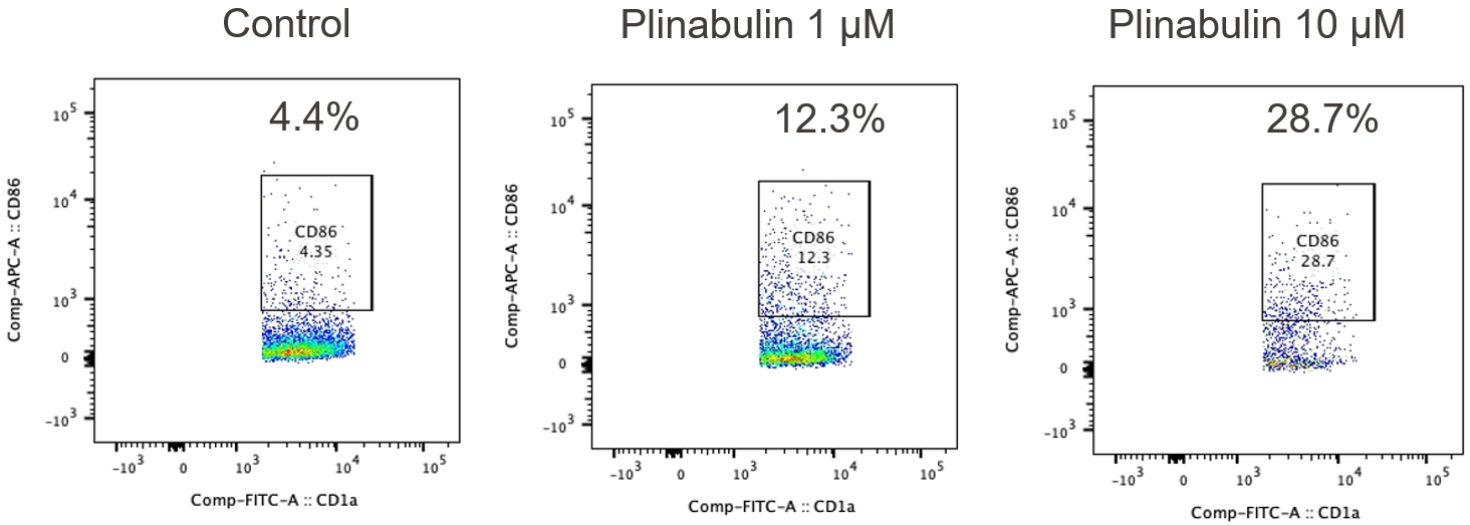


Plinabulin stim CD86, PD-L1 in human PBMCs derived DCs

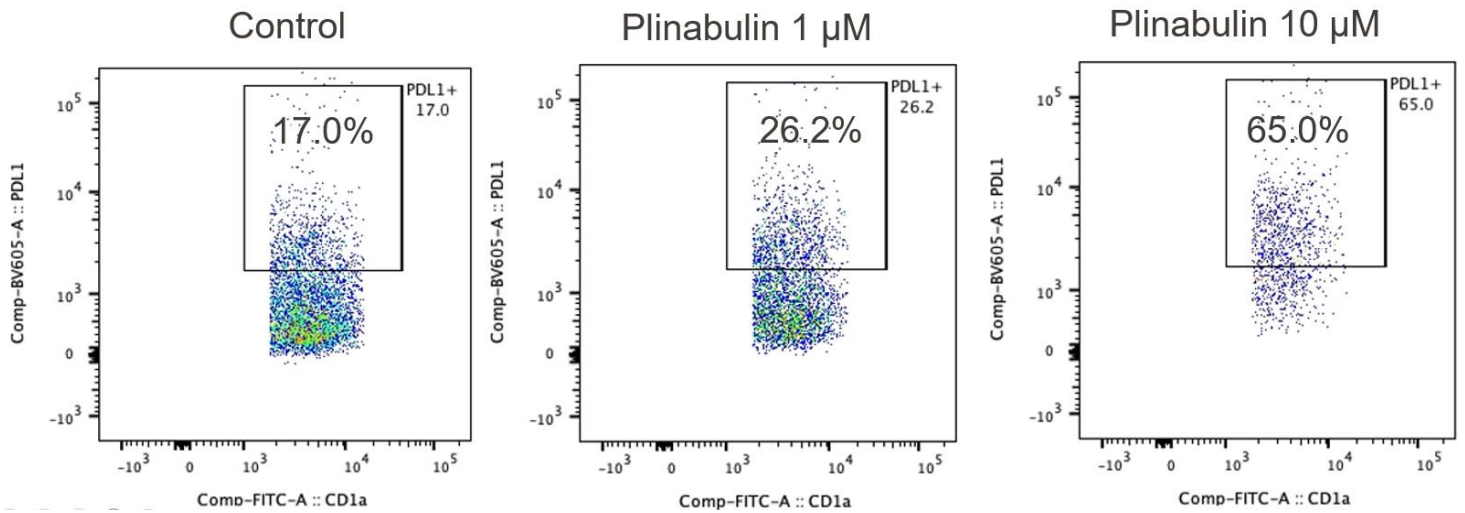




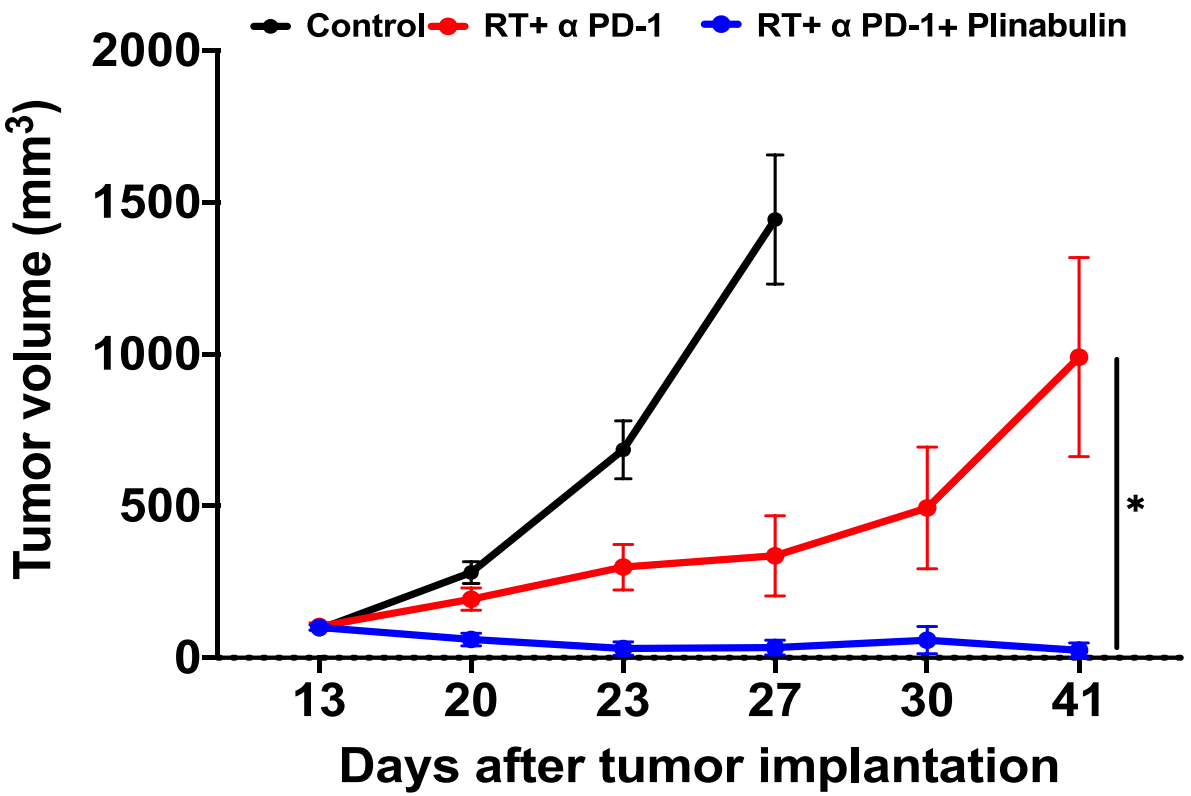
CD86



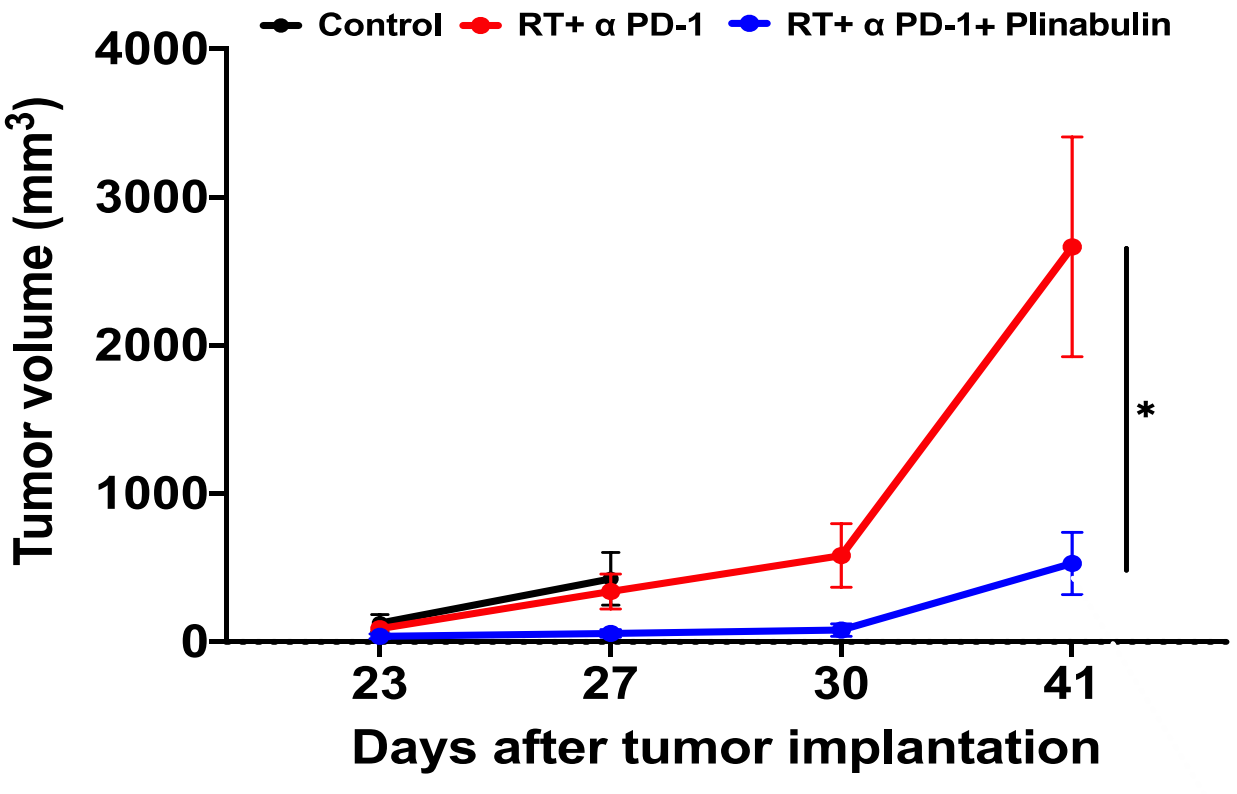
PD-L1



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

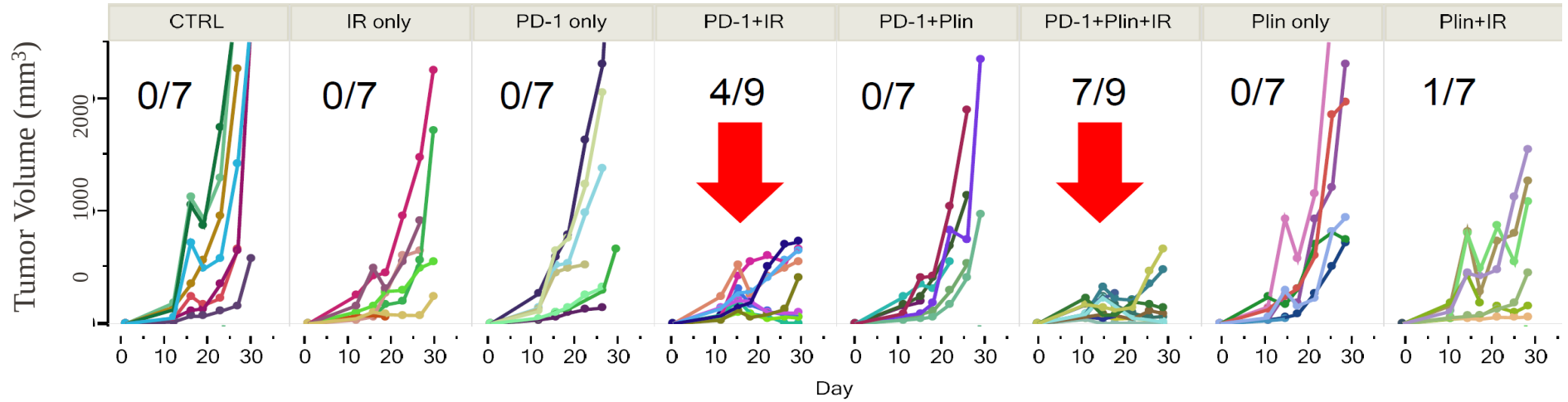


Primary tumor



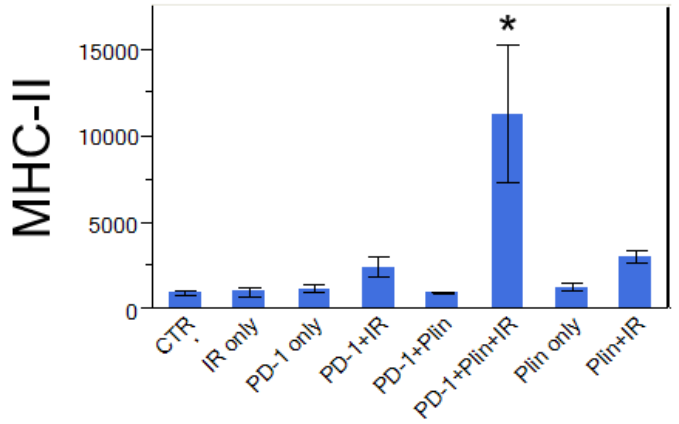
Abscopal tumor

Plinabulin + RT increases PD-1 systemic and immunologic response

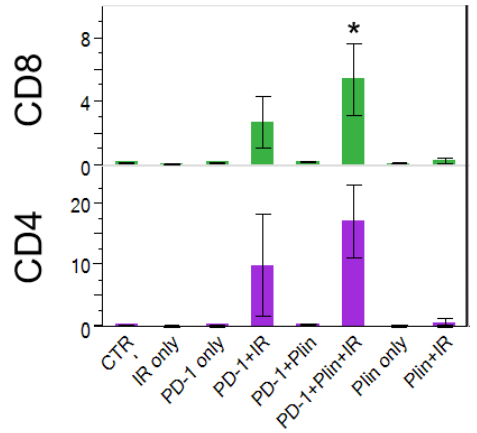


"Abscopal Tumor"

DC activation is most dramatic in triple I/O combination



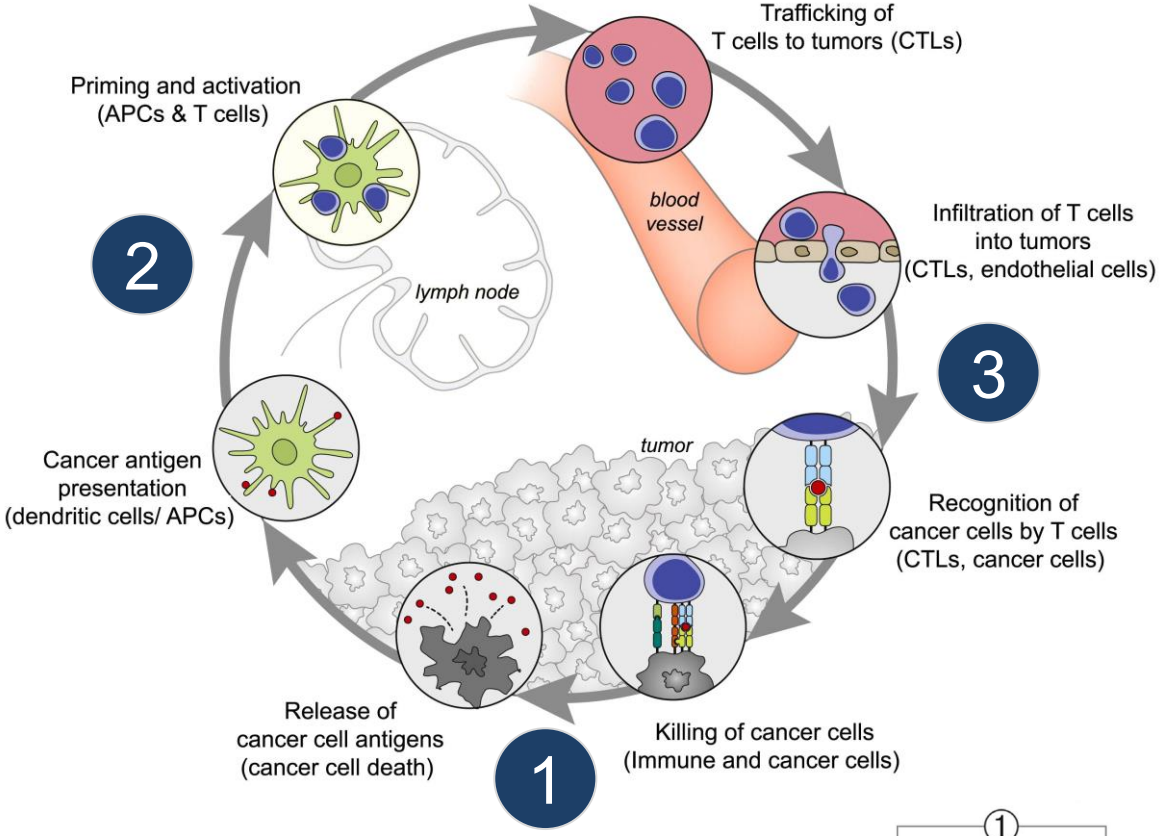
T cell doubles in triple I/O combination vs. PD1 + IR



Plinabulin Enhances the Cancer Immunity Cycle When Used with Radiation/Chemotherapy and Anti-PD1

② Plinabulin

Improved antigen presentation
Stimulate maturation of dendritic cells (DC) 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

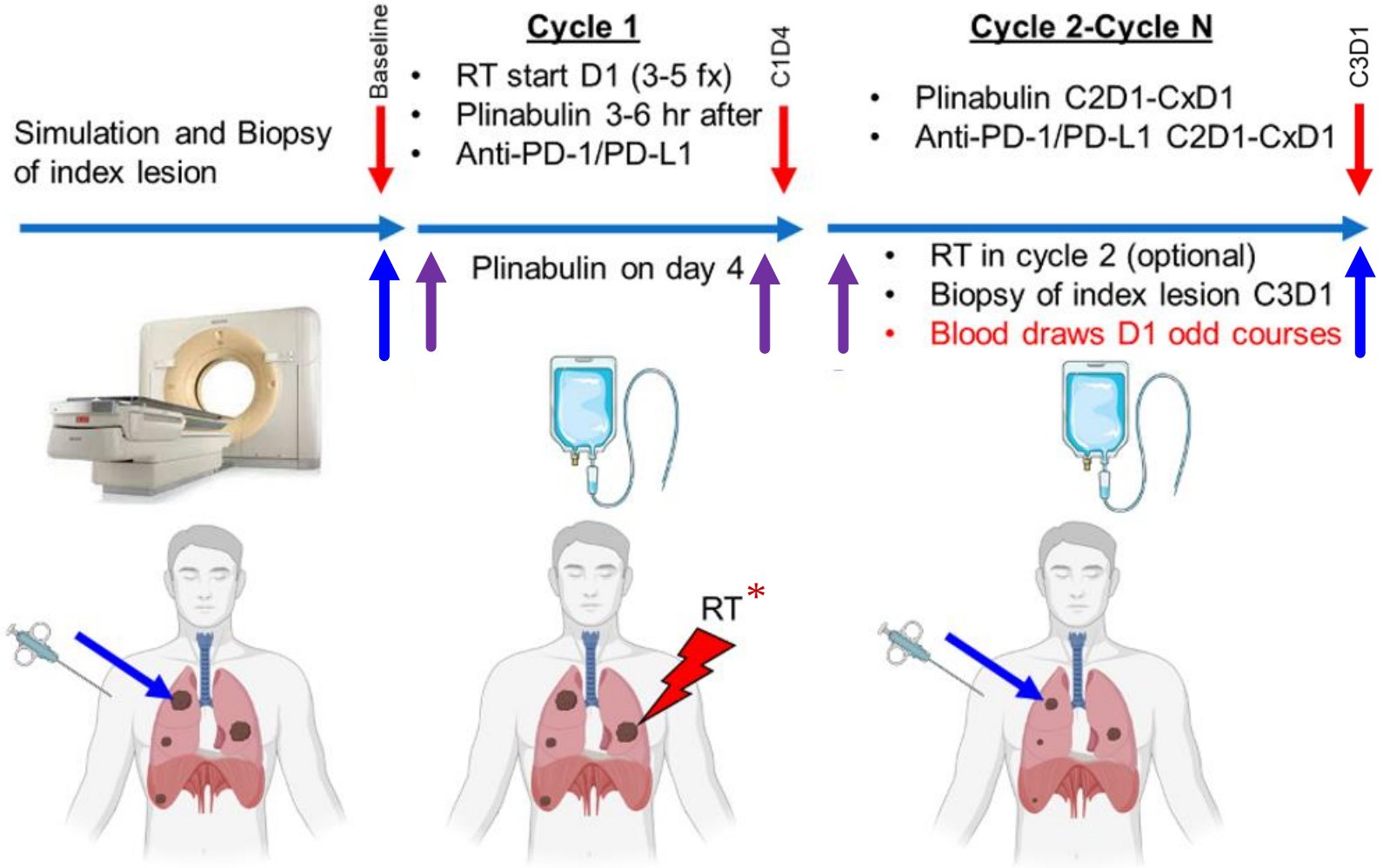
1. Mellman I, et al. Immunity 2023

2020-0296: Phase 1b/2 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

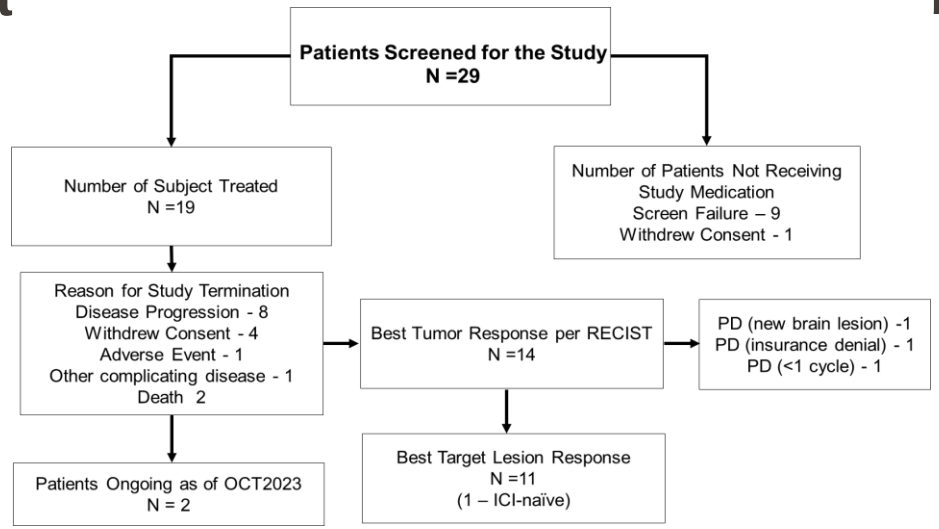
Study Design:
Open label, single-center
Phase Ib
3+3 design, DLT w/in 30 days



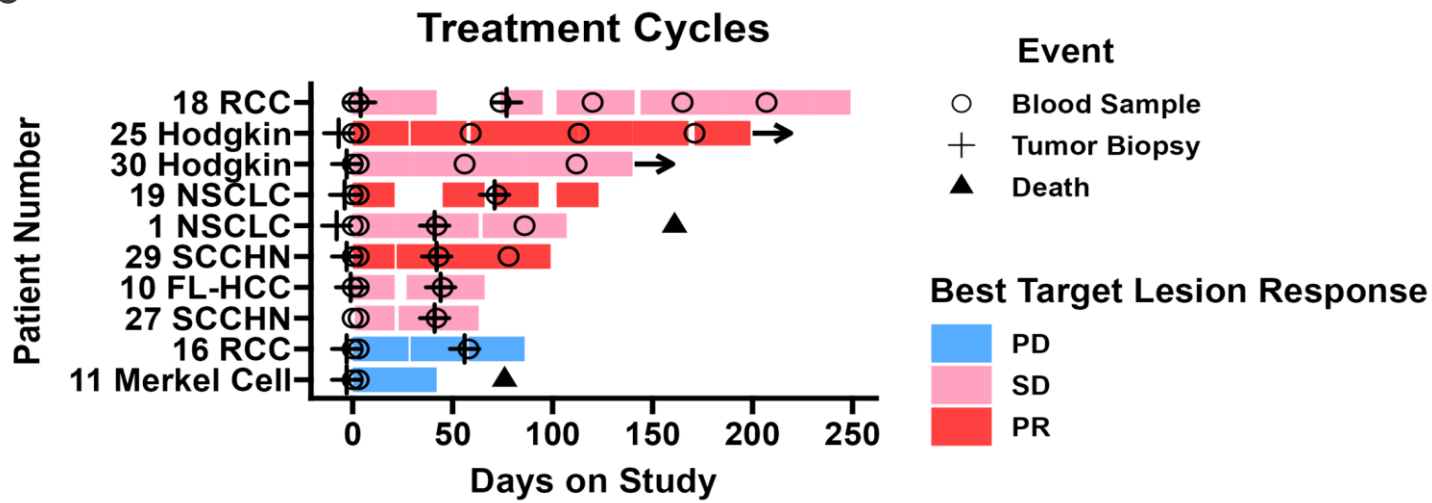
*** RT = 24 Gy/3 fx; 50 Gy/4 fx; 20 Gy/5 fx**

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

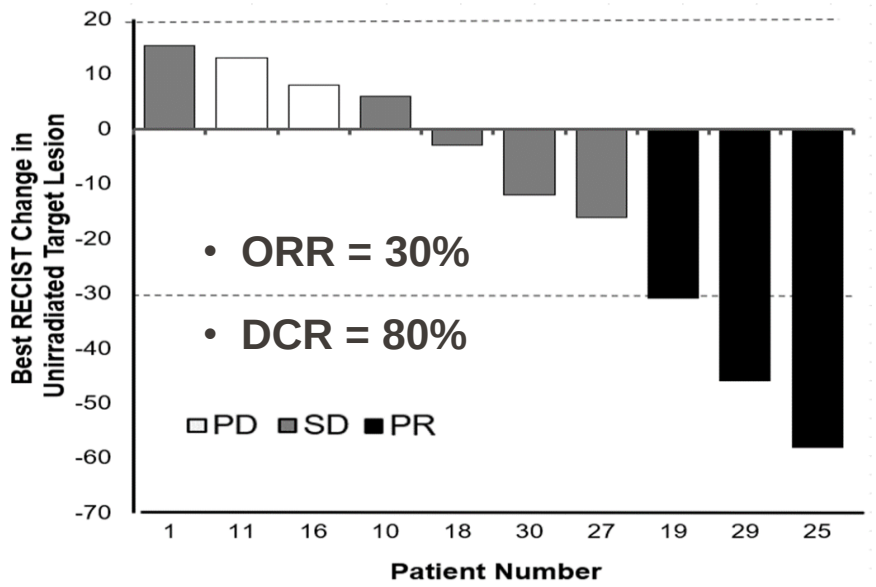
a


Patients Screened for the Study
N =29
Number of Subject Treated
N =19
Number of Patients Not Receiving
Study Medication
Screen Failure – 9
Withdrew Consent - 1
Reason for Study Termination
Disease Progression - 8
Withdrew Consent - 4
Adverse Event - 1
Other complicating disease - 1
Death 2
Best Tumor Response per RECIST
N =14
PD (new brain lesion) -1
PD (insurance denial) - 1
PD (<1 cycle) - 1
Patients Ongoing as of OCT2023
N = 2
Best Target Lesion Response
N =11
(1 – ICI-naïve)

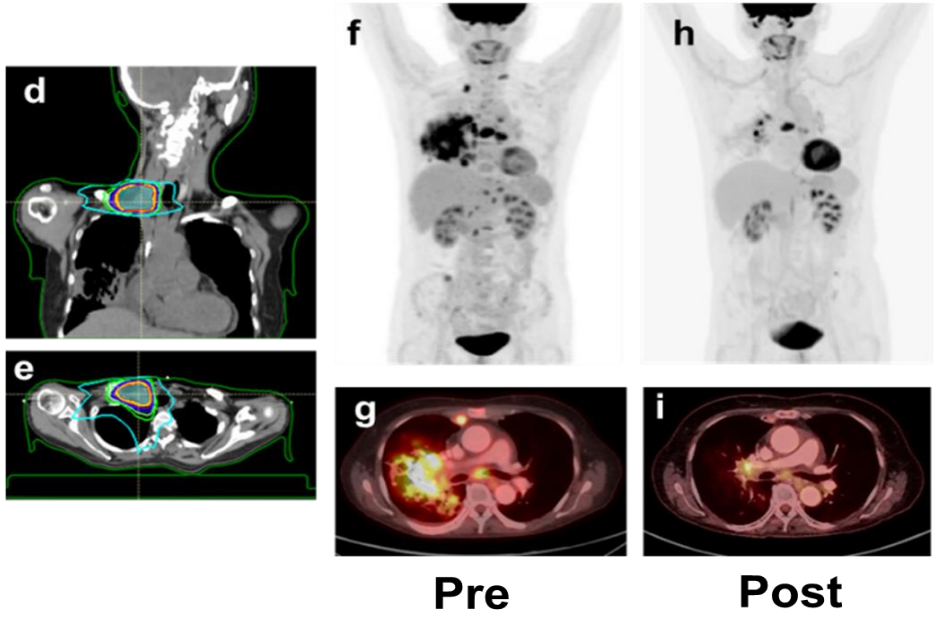
b


Treatment Cycles
Patient Number
18 RCC
25 Hodgkin
30 Hodgkin
19 NSCLC
1 NSCLC
29 SCCHN
10 FL-HCC
27 SCCHN
16 RCC
11 Merkel Cell
0
50
100
150
200
250
Days on Study
Event
Blood Sample
Tumor Biopsy
Death
Best Target Lesion Response
PD
SD
PR

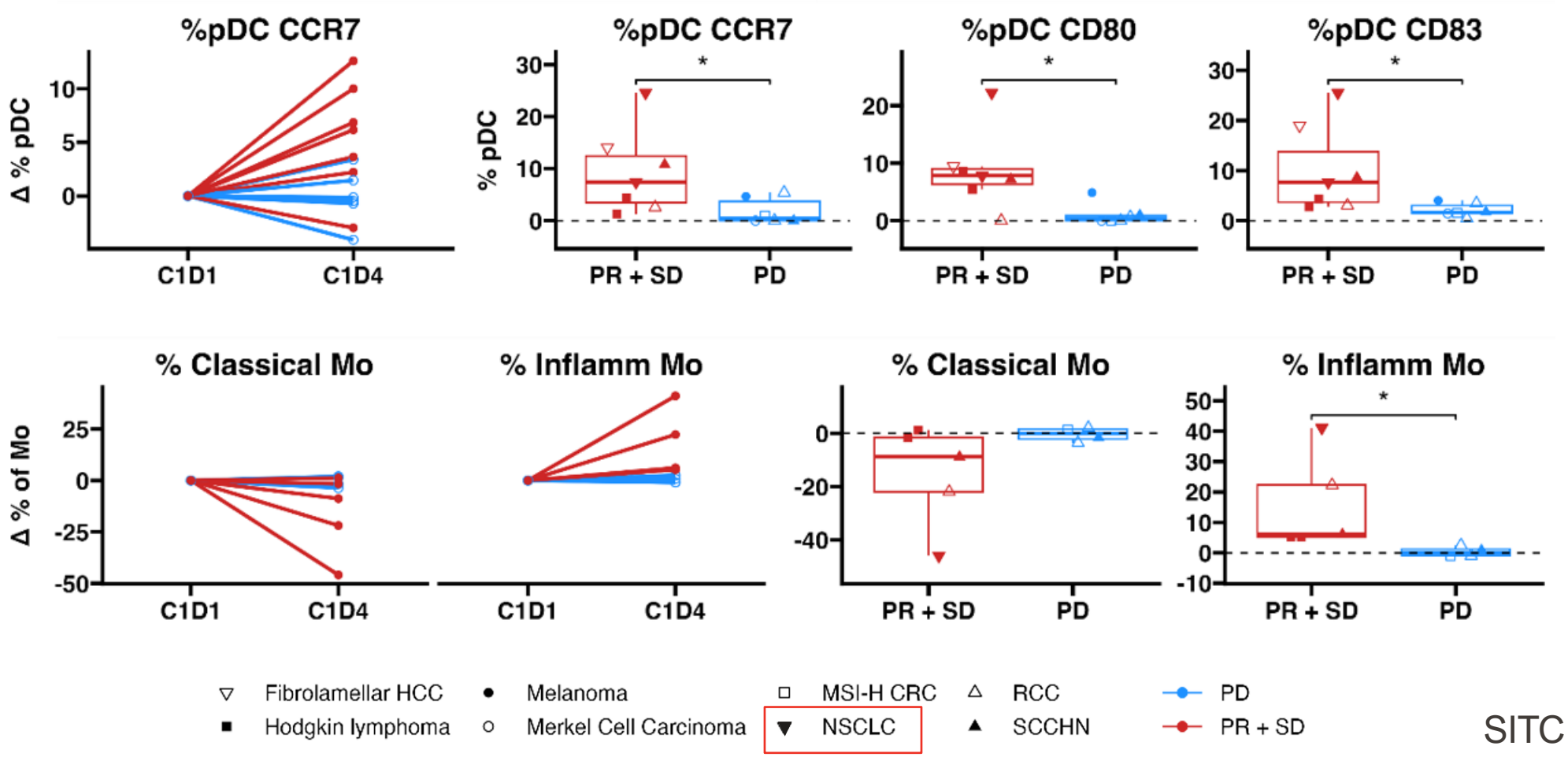
c


Best RECIST Change in Unirradiated Target Lesion
20
10
0
-10
-20
-30
-40
-50
-60
-70
• ORR = 30%
• DCR = 80%
PD SD PR
1
11
16
10
18
30
27
19
29
25
Patient Number

d

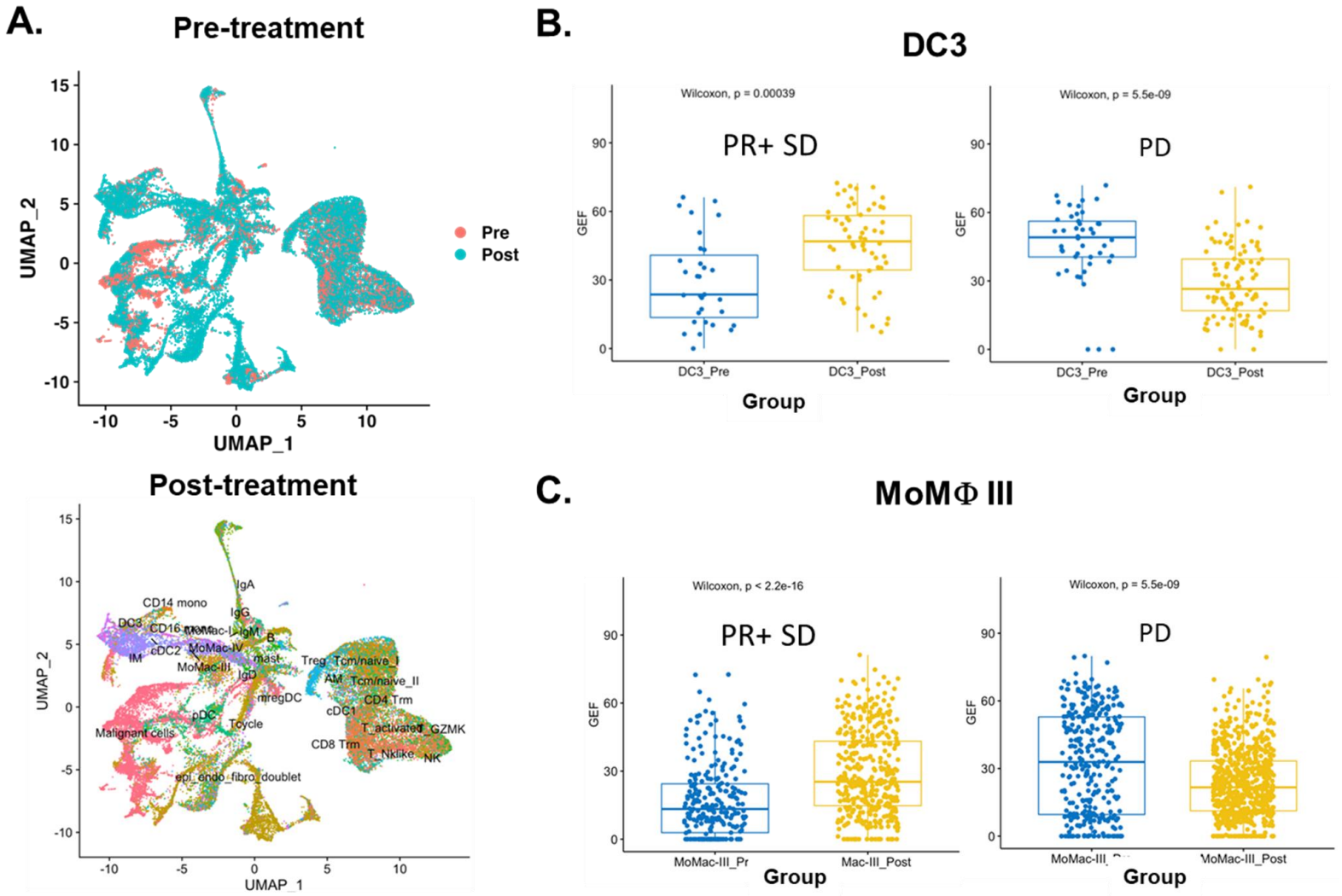

d
e
f
h
g
i
Pre
Post

Significant increase in activated and CCR7+ DCs in peripheral blood on C1D4 with RT + plinabulin in PR+SD vs PD pts



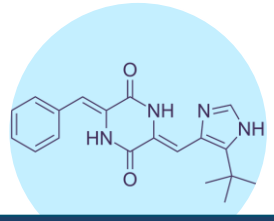
SITC 2023

Tumor scRNA seq reveals conducive TME for plinabulin/RT/anti-PD1 response in responder group



SITC 2023

Plinabulin, Combined with Radiation and Immune Checkpoint Inhibitors, Induces DC Maturation and Potentially Re-sensitizes IO-failure Tumors to Immune Checkpoint Blockade



Plinabulin is a Unique Tubulin Binder

Plinabulin's tubulin binding site is distinct from that of other tubulin binding agents such as taxanes, vinca alkaloids, and colchicine.

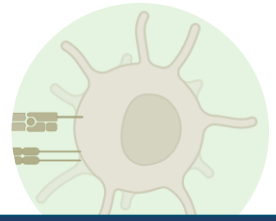
Strong Preclinical Proof of Concept

Plinabulin in combination with radiation and anti-PD-1 **activates DCs, stimulates T-cell proliferation**, and achieves **abscopal effects**.

Clinical Evidence of Efficacy

In 10 IO-relapsed patients, >50% disease control rate and durable responses in heavily pre-treated patients,

Potential in **clinical efficacy in a growing high-unmet need IO-failed population**.



Clinical Evidence of Immune Activation

Responding patients exhibit early immune activation with DC maturation.

These IO effects are observed across multiple different cancer types, NSCLC, HNSCC and Hodgkin's Lymphoma, indicating **broad applicability**.

Plinabulin is Being Evaluated in Combination with Pembrolizumab and Docetaxel in 2L/3L NSCLC after PD-1/L1 Failure (Recruiting in China)

An Open-Label, Single-Arm, Phase II Investigator-Initiated Study (KeyPemIs-004; NCT05599789)

Study Plan

- Estimated: 47 participants; futility analysis n=19
- First patient dosed: March 1, 2023
- Pembrolizumab 200 mg D1 Q3W (up to 35 cycles)
- Docetaxel 75 mg/m2 D1 Q3W (until PD, untolerable SAE, or withdraw from patient)
- Plinabulin 30mg/m2 D1 Q3W (until PD, untolerable SAE, or withdraw from patient)

Primary Endpoint

- **ORR (RECIST 1.1)**

Secondary Endpoints

- PFS (RECIST 1.1)
- OS
- DOR
- OS rate
- Safety

PD-1/PD-L1 failed patients in NSCLC:
Current SOC: mPFS = 3-4 months; ORR: around 10%

Inclusion Criteria:

- Metastatic NSCLC
- Progressed on anti-PD-1/L1 monotherapy or in combo with platinum-doublet
- 1L PFS > 6 months
- ECOG PS 0-1
- Must have measurable disease

Exclusion Criteria:

- Prior use of docetaxel or plinabulin
- Need to use steroid to treat ILD, or pneumonia
- Need to use EGFR, ALK, or ROS1-target therapy as primary treatment
- Brain metastasis, or leptomeningeal metastasis

BeyondSpring

BeyondSpring

Unmet Need, Combination Strategies and ICI Resistance in ES-SCLC

Alberto Chiappori, MD

Moffitt Cancer Center

Leading Expert Speaker Biography

Dr. Alberto Chiappori, Moffitt Cancer Center

Dr. Alberto Chiappori currently serves as Senior Member of Oncology and Medicine for the Thoracic Oncology Program at the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida, and has been a member of the Thoracic Oncology Program at Moffitt since 2001.

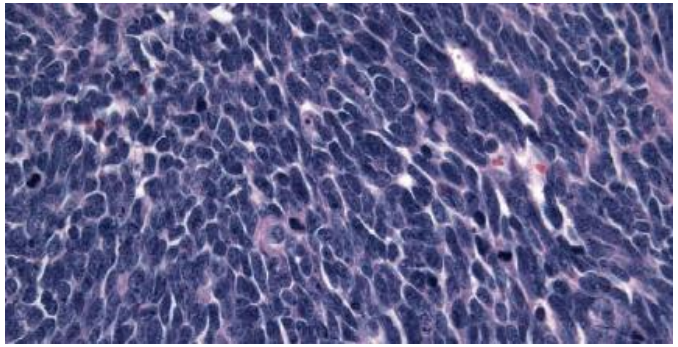
Dr. Chiappori received his MD from the Universidad Peruana Cayetano Heredia in Lima, Peru. After graduation, he completed his residency at Southern Illinois University School of Medicine in Springfield, Illinois. He then went on to finish his fellowship and senior fellowship in medical oncology-hematology at Vanderbilt University School of Medicine in Nashville, Tennessee.

Dr. Chiappori has been Board Certified in Medical Oncology since 1997. Dr. Chiappori has coauthored numerous articles in journals including Clinical Cancer Research, Journal of Thoracic Oncology, and Journal of Clinical Oncology. He is also an active member of the American Society of Clinical Oncology, the European Society of Medical Oncology, the American Association for Cancer Research and the International Association for the Study of Lung Cancer (IASLC).

SCLC Pathology
Spectrum of Neuroendocrine Carcinomas (NEC)

- SCLC presents as malignant, epithelial, high-grade, neuroendocrine tumors[1,2]
  - Markers of epithelial origin
  - Neuroendocrine and neural differentiation markers: synaptophysin, chromogranin A, CD56
- SCLC falls along spectrum of WHO classification of neuroendocrine lung tumors[2,3]
- Potential therapeutic Implications

HPF View of SCLC Tumor[1]



WHO Classification[2,3]	Mitoses/ 10 HPF	Necrosis	Cytologic Features
Typical carcinoid	< 2	None	--
Atypical carcinoid	2-10	Generally punctate	--
Small-cell carcinoma	> 10	Generally abundant	Small size, scant cytoplasm, finely granular chromatin, faint nucleoli
Large-cell neuroendocrine carcinoma	> 10	Generally abundant	Cytologic features opposite SCLC

1. Jackman DM, et al. Lancet. 2005;366:1385-1396. 2. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. 2015. 3. Rossi G, et al. Curr Opin Pulm Med. 2014;20:332-339.

SCLC Diagnosis and Staging

- Diagnosis by FNA or biopsy
- Staging work-up
  - CT chest/abdomen/pelvis
  - Brain MRI
  - PET scan to rule out distant metastases
  - Further workup to rule out nodal involvement and/or distant metastases as clinically indicated

- TNM staging system vs VA Lung Study Group staging system

TNM Staging	VALSG Staging	Incidence
T1-T2, N0, M0 (stage I)	Limited stage	~ 5%
T any, N any, M0 (stage I-III)	Limited stage; disease burden contained within radiation field	~ 30%
T any, N any, M1 (stage IV)	Extensive stage; disease burden beyond radiation field	~ 65%

- TNM staging system is rarely used

Kalemkerian GP. Cancer Imaging. 2011;11:253-258. Alvarado-Luna G, et al. Transl Lung Cancer Res. 2016;5:26-38. Sabari JK, et al. Nat Rev Clin Oncol. 2017;14:549-561.

Extensive-Stage SCLC:

First-line Chemotherapy

- SoC: Platinum and etoposide for 4-6 cycles[1]
- Efficacy:
  - Response rates: ~ 50% to 70%
    (CR~10-20%, PR~40-50%)
  - 2-yr OS: < 5%
  - Median PFS: 2-4 mos
  - Median OS: 9-11 mos
- Meta-analysis of 4 trials comparing cisplatin- vs carboplatin-based regimens (N = 663)[2]
  - No differences in OS, PFS, ORR

Study	Cisplatin/ Irinotecan	Cisplatin/ Etoposide
Noda[3]	(n = 77)	(n = 77)
▪ mOS, mos*	12.8	9.4
▪ 2-yr OS, %	19.5	5.2
Hanna[4]	(n = 221)	(n = 110)
▪ mOS, mos	9.3	10.2
▪ ORR, %	48	43.6
▪ Toxicities	More vomiting, diarrhea	More anemia, neutropenia, thrombocytopenia

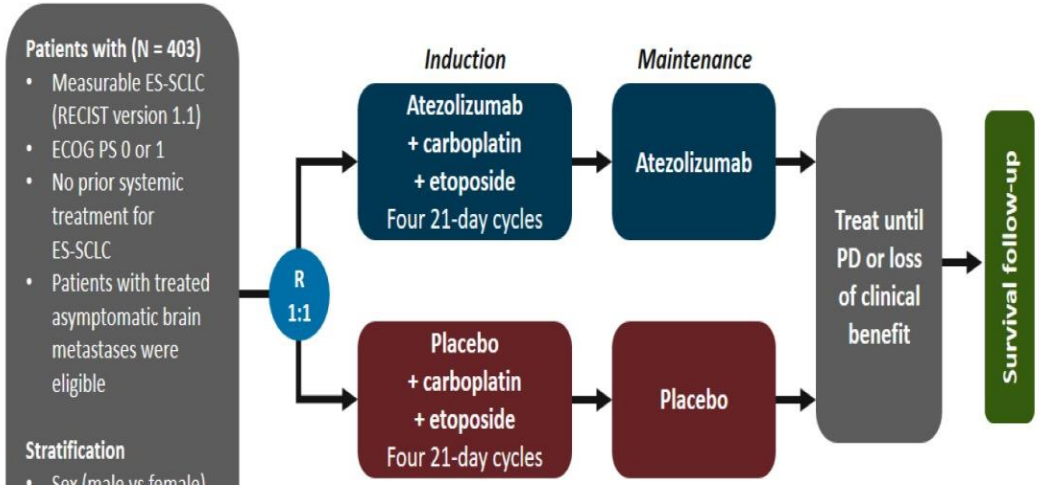
Inevitably, ALL patients progress: Recurrent disease

1. Bernhardt EB, et al. Cancer Treat Res. 2016;170:301-322. 2. Rossi A, et al. J Clin Oncol. 2012;30:1692-1698. 3. Noda K, et al. N Engl J Med. 2002;346:85-91. 4. Hanna N, et al. J Clin Oncol. 2006;24:2038-2043.

ES-SCLC Immunotherapy: New First Line Standard

First-Line Treatment: IMpower133

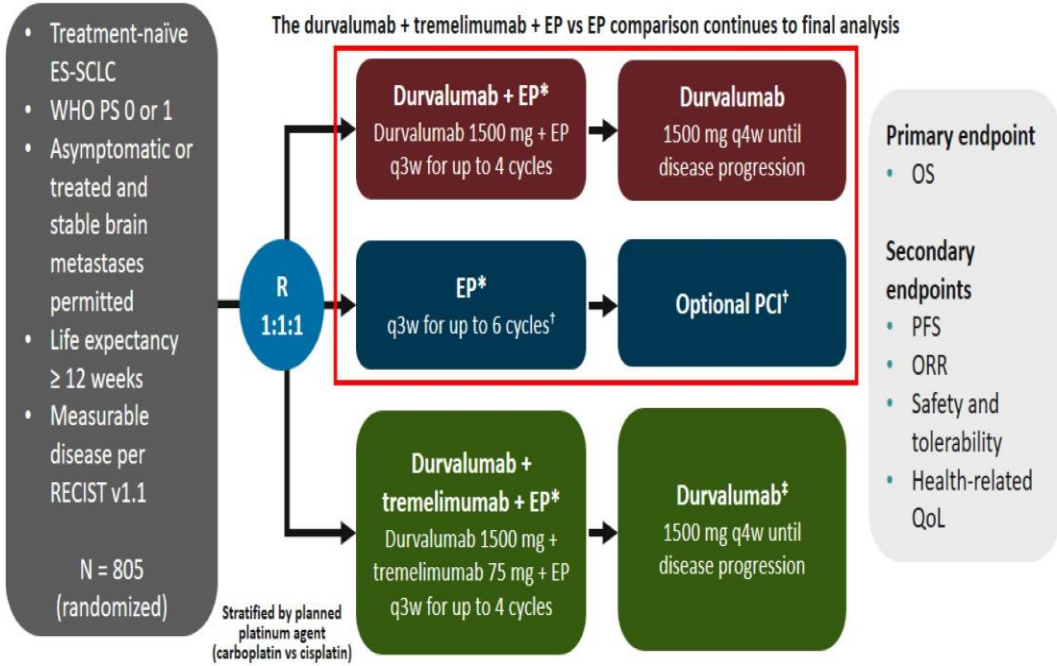
Study Design



Note: Atezolizumab, 1200 mg IV, Day 1; Carboplatin, AUC 5 mg/mL/min IV, Day 1; Etoposide, 100 mg/m 2 IV, Days 1–3.
*Only patients with treated brain metastases were eligible.
Horn L, et al. *N Engl J Med*. 2018;379:2220-2229; Reck M, et al. ESMO 2019. Presentation 1736O.

First-Line Treatment: CASPIAN

Study Design



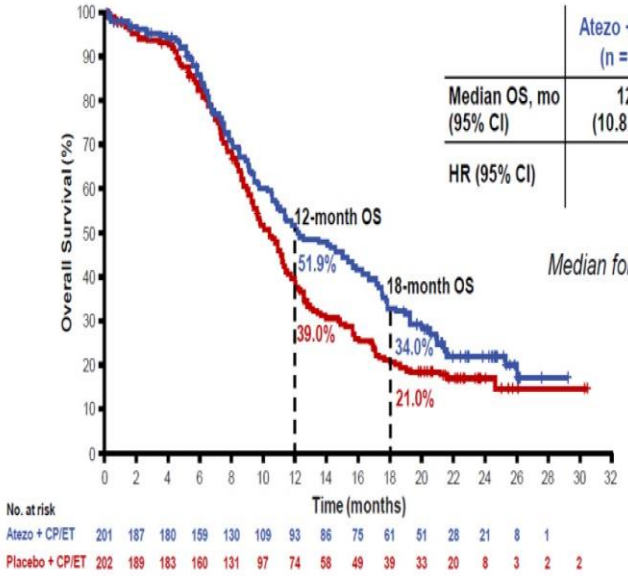
*EP consists of etoposide 80–100 mg/m² with either carboplatin AUC 5-6 or cisplatin 75-80 mg/m²; †Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion; ‡Patients received an additional dose of tremelimumab post-EP.
Paz-Ares L, et al. *Lancet*. 2019;394:1929-1939; Paz-Ares L, et al. WCLC 2019. Presentation PL02.11.

Extensive-Stage-SCLC Chemo-Immunotherapy:

New First Line Standard

First-Line Treatment: IMpower133

Updated Results



	Atezo + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
Median OS, mo (95% CI)	12.3 (10.8, 15.8)	10.3 (9.3, 11.3)
HR (95% CI)	0.76 (0.60, 0.95) p = 0.0154[a]	

Median follow-up, 22.9 months

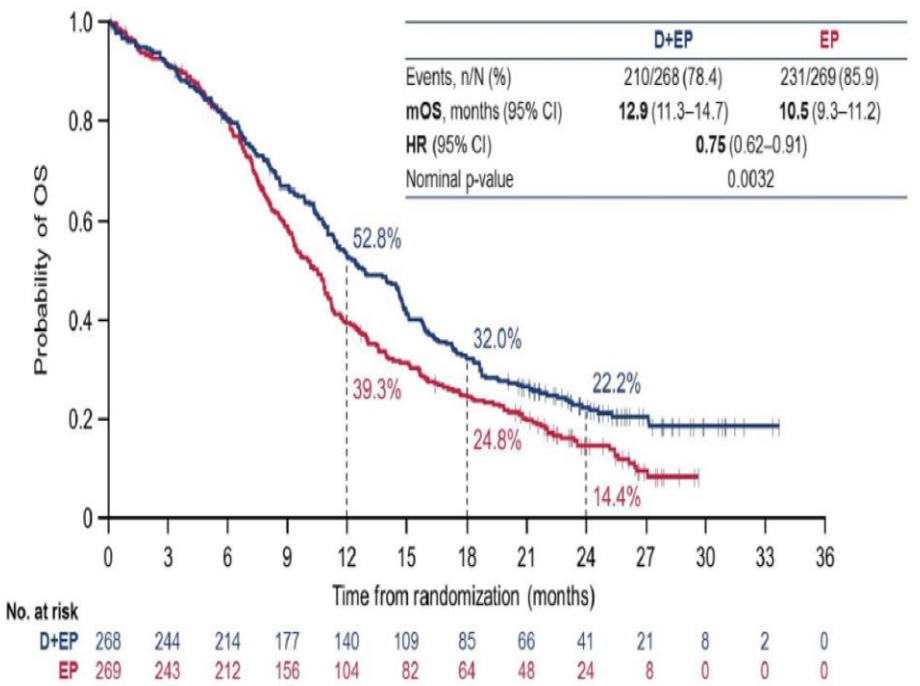
[a]p-value is provided for descriptive purpose.
CCOD 24 January 2019

Endpoint	Atezo + CP/ET (n = 201)	Placebo + CP/ET (n = 202)
ORR, %	60.2	64.4
mDOR, mo	4.2	3.9

Reck M, et al. ESMO 2019. Presentation 1736O.

First-Line Treatment: CASPIAN

Updated OS



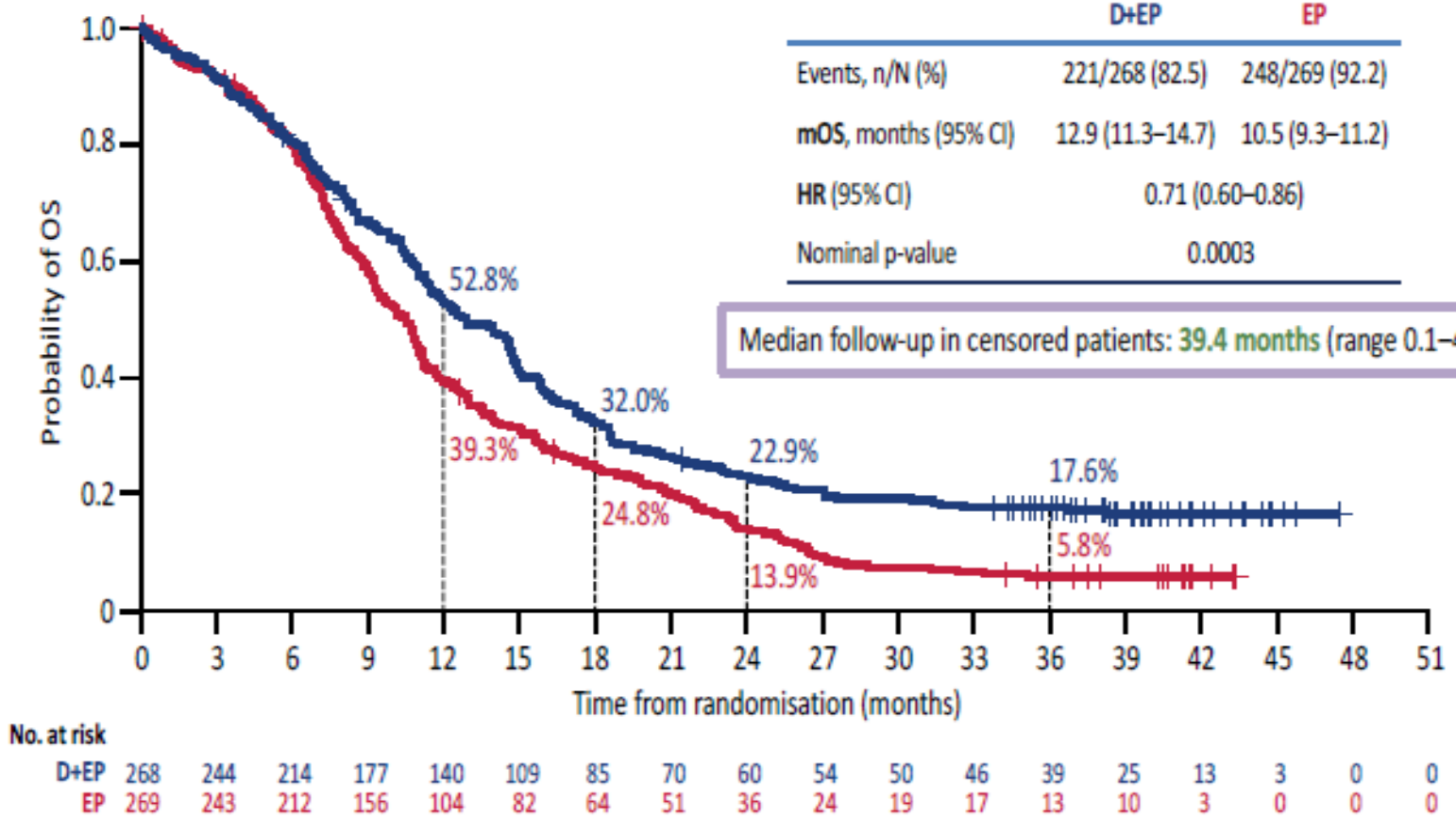
	D+EP	EP
Events, n/N (%)	210/268 (78.4)	231/269 (85.9)
mOS, months (95% CI)	12.9 (11.3–14.7)	10.5 (9.3–11.2)
HR (95% CI)	0.75 (0.62–0.91)	
Nominal p-value	0.0032	

Paz-Ares L, et al. ASCO® 2020. Presentation 9002.

First Line Therapy, ES-SCLC

Chemo-Immunotherapy Trials

3-year Overall Survival Update: D+EP vs EP



	D+EP	EP
Events, n/N (%)	221/268 (82.5)	248/269 (92.2)
mOS, months (95% CI)	12.9 (11.3–14.7)	10.5 (9.3–11.2)
HR (95% CI)	0.71 (0.60–0.86)	
Nominal p-value	0.0003	

Median follow-up in censored patients: 39.4 months (range 0.1–47.5)

Paz-Ares, L. ESMO Open 2022

First Line Therapy, ES-SCLC

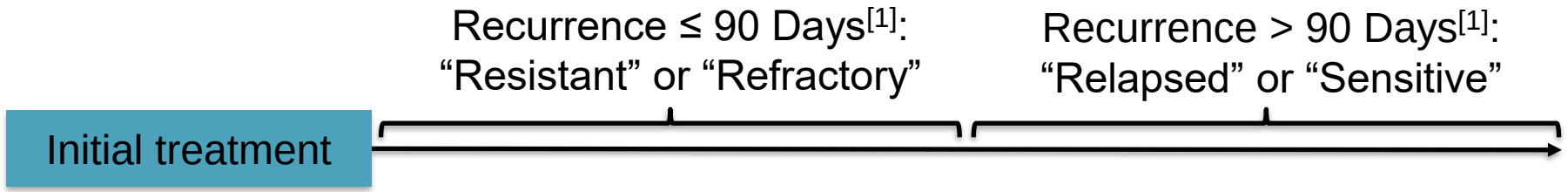
Chemo-Immunotherapy Trials

Addition of immune checkpoint blockade to chemotherapy is a new standard of care for ES-SCLC

1L ES-SCLC Chemo-IO Trial	Combination	ASCO Abstract	Status	Outcome Data
IMPower133	EP + atezolizumab	--	FDA Approved	mOS 12.3mo (EP-atezo) vs 10.3mo (EP-placebo) (HR 0.70)
CASPIAN	EP + durvalumab	**ASCO 9002**	FDA Approved	mOS 12.9mo (EP-durva) vs 10.5mo (EP) (HR 0.75)
Keynote-604	EP + pembrolizumab	**ASCO 9001**		mOS 10.8mo (EP-pembro) vs 9.7mo (EP) (HR 0.80 in IA2, NS; HR=0.75 in post-hoc "as treated analysis)
ECOG-ACRIN EA5161 **Randomized Ph2**	EP + nivolumab	**ASCO 9000**		mPFS 5.5mo (EP-nivo) vs 4.6mo (EP) (HR 0.65); mOS 11.3mo vs 8.5mo (HR 0.67)

*EP = platinum-etoposide

Second-line Management of Recurrent SCLC



- Topotecan is the only FDA-approved second-line therapy for sensitive or relapsed SCLC
  - 1.5 mg/m^2 IV on Days 1-5 of a 21-day cycle[2]
  - Oral topotecan: significant activity; improved OS and symptom control vs best supportive care[3]
- Other recommended second-line agents include:[1]
  - CAV, irinotecan, paclitaxel, docetaxel, temozolomide, gemcitabine, ifosfamide, vinorelbine
- Original regimen can be given if relapse > 6 mos
- Clinical trial is preferred

1. Schmittel A. Expert Rev Anticancer Ther. 2011;11:631-637. 2. Ardizzoni A, et al. J Clin Oncol. 1997;15:2090-2096. 3. O'Brien ME, et al. J Clin Oncol. 2006;24:5441-5447.

Plinabulin is Being Evaluated in Combination with Pembrolizumab and Etoposide/Platinum in First-Line ES-SCLC (Recruiting in China)

An Open-Label, Single-Arm, Phase II Investigator-Initiated Study (NCT05745350)

Study Plan

- Estimated: 45 participants
- First patient dosed: March 25, 2024
- Pembrolizumab 200 mg IV every 3 weeks (Q3W) on Day 1
- Etoposide 100 mg/m2 IV Q3W on Days 1, 2, 3
- Carboplatin AUC 5 IV Q3W on Day 1 or Cisplatin 75 mg/m2 IV Q3W on Day 1
- Plinabulin 30mg/m2 IV Q3W on Day 1.

Primary endpoint

12-month PFS rate

Secondary endpoints

- ORR
- DoR
- PFS
- OS
- TRAE (CTCAE v5.0)
- Exploratory Biomarker Research (blood and/or tissues)

KEYNOTE-604 study:
12-month PFS rate in patients with pembrolizumab plus EP is 13.6% vs. 3.1% with placebo plus EP.

Inclusion Criteria:

- Newly diagnosed SCLC
- Stage IV
- ECOG o or 1
- Life Expectance ≥3 months
- Must have at least one measurable tumor lesion

Exclusion Criteria:

- Prior radiotherapy within 2 weeks
- Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (ie, CTLA-4, OX-40, CD137) or has previously participated in an MSD pembrolizumab (MK-3475) clinical trial and BeyondSpring Plinabulin clinical trial.

BeyondSpring

BeyondSpring

SEED Therapeutics

SEED Therapeutics: Targeted Protein Degradation Molecular Glue R&D

A global leader in Targeted Protein Degradation (TPD) with deep expertise to address its key challenges

- TPD can target 80% of the disease-causing proteins that were “undruggable”. All top-20 global pharma have TPD development programs internally and/or though high value licensing and acquisitions
- Deploy multi-dimensional proprietary platform to identify the right E3 for Protein of Interest

Early validation and funding from Eli Lilly partnership

- Started joint TPD development with Eli Lilly shortly after inception, focusing on **multiple pre-selected POIs by Lilly**
- Address some most challenging POIs with $10m upfront and milestone payment up to **$780m** plus tiered royalties. Lilly also made a $10m equity investment in SEED with an equity share of 19.9% post investment. BeyondSpring holds a 60.1% equity stake in SEED
- Our R&D program with Lilly has exceeded expectations with three milestone payments received

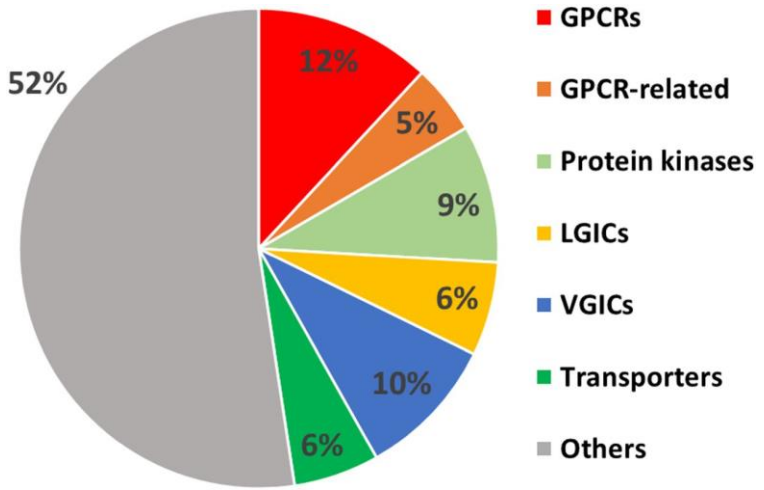
Diversified and fast evolving internal pipeline

- Have developed **8 programs** across oncology, neurodegeneration, immunology, and antiviral indications over 3 years, including 6 internal programs and involving **5 novel E3s**
- Lead program, a **RBM39 Oral Degrader** addresses a highly validated biology target with multi billion-dollar market potential and "**First to Market, Best in Class**" profile. Target first human dose (FHD) in 1H2025

Targeted Protein Degradation (TPD) Addresses 80% of Disease-Causing Proteins That Are Undruggable

TPD for Undruggable Proteins

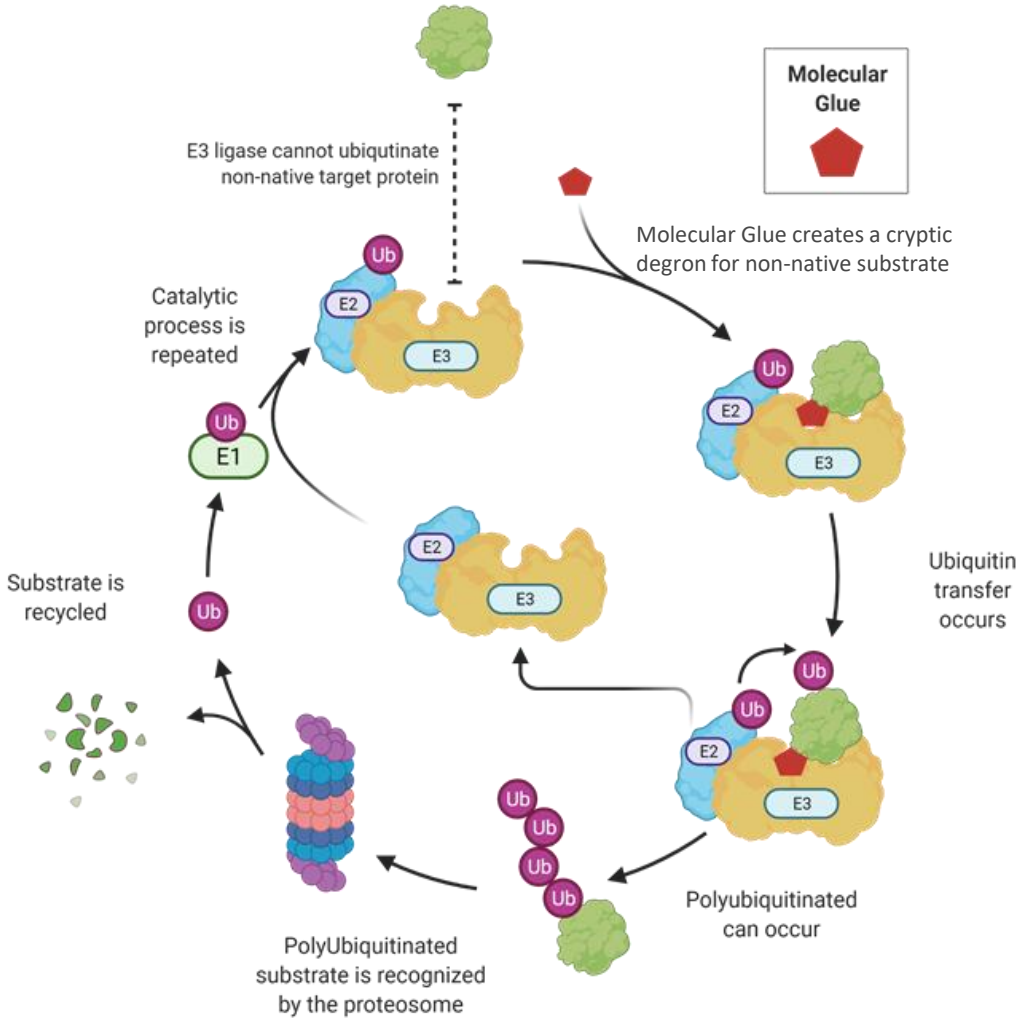
Druggable Proteins



Sriram et al., Molecular Pharmacology, 2018

TPD Development History and Recent Renaissance

TPD Process

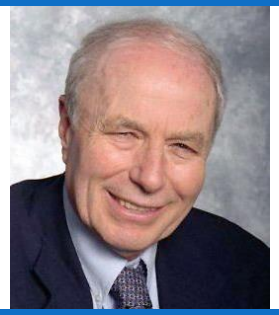


SEED Co-founders played pivotal roles in the advancement of TPD field

- 1996: **Dr. Michele Pagano (SEED co-founder)** discovered cell cycle regulation by TPD, including E3 ligases; published in *Science*
- 1999: **Dr. Lan Huang (SEED co-founder and CEO)** solved the 1st of the two E3 structures (HECT domain E3); published in *Science*
- 2002: **Dr. Ning Zheng (SEED co-founder)** solved the 2nd of the two E3 structure (Ring-finger E3); published in *Nature*
- 2003: US FDA approved **Velcade**, the first proteasome inhibitor for multiple myeloma. **Dr. Avram Hershko (SEED co-founder)** 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 proteasome
- 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**.

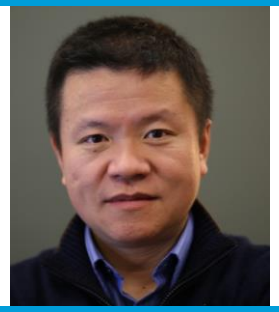
World Class Leadership Team and Exceptional Insights in TPD Drug R&D

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 members for Eli Lilly, HSBC, Mastercard; former DBS Bank CEO, former J.P. Morgan & Co, investment banker

BeyondSpring

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

Highly Experienced in-House R&D Team

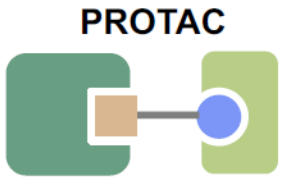
Discovery Labs, City of Science, King of Prussia, PA

- 10,000 ft^2 including 7000 ft^2 lab space
- All crucial discovery work are 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 IND filings**
- **>12 drug approvals**, including multiple biologics and the small molecules Paritaprevir, Glecaprevir, XERMELO, REZUROCK, GV-971 and Modafinil

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:

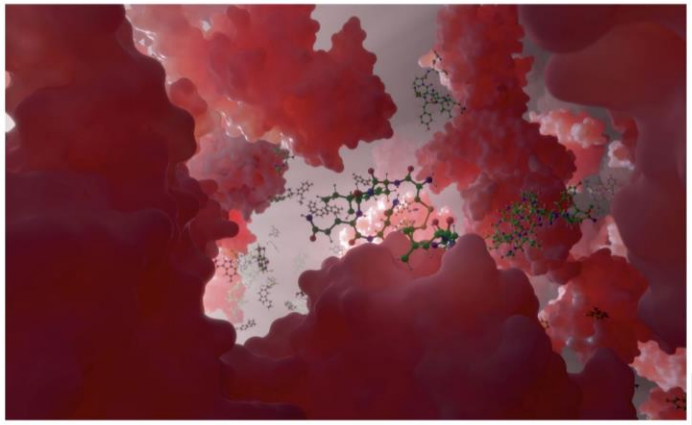
- ✓ Involves a single non-chimeric small molecule
- ✓ Small enough to be drug-like compounds
- ✓ Does not need high affinity on either sides (ligandable pockets not required)
- ✓ Many UBLs can be used (Substrate-centric)

1. PROTAC, lead asset in phase 3 development, validates the TPD field;
2. High value companies in PROTAC companies, including Arvinas and Kymera ($>2 B market cap)

“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.

SEED was prominently featured in “Nature Biotechnology” Review.

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

Table 1 | Selected molecular glue degrader companies discussed

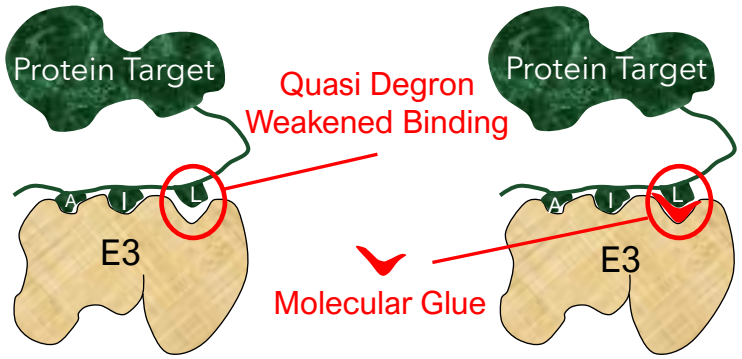
Company	Pharma partners	Discovery approach	Deployed E3 ligases	Lead program
Monte Rosa Therapeutics	Roche	Remodel cereblon to recruit neosubstrates; proximity assays, proteomics	Cereblon	MRT-2359, GSPT1 degrader, phase 1 (cancer)
Plexium	Amgen, AbbVie	Miniaturized, cell-based DNA-encoded library screening; 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.

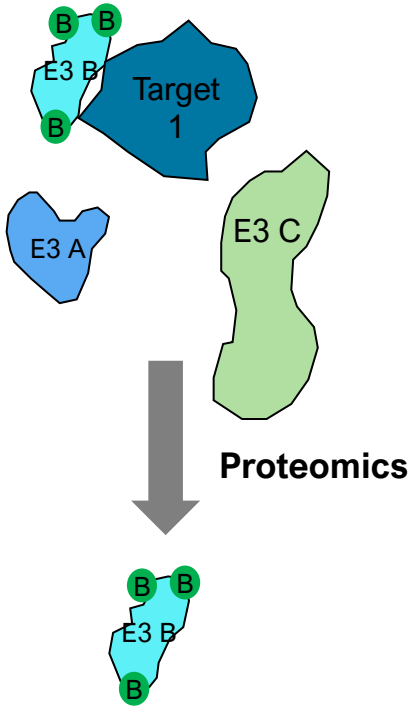
Garber, *Nature Biotechnology* (2024)

Multi-Dimensional and Proprietary Platform for E3 Selection

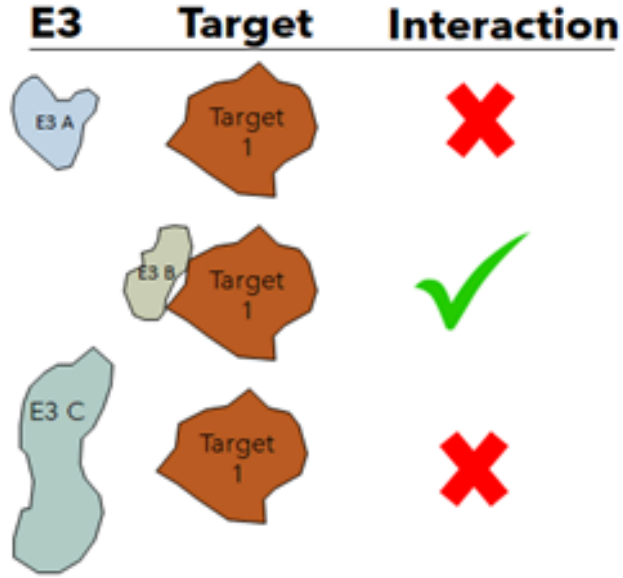
Quasi-Interface Analyses



LumID: identify the right E3 near POI in live cell

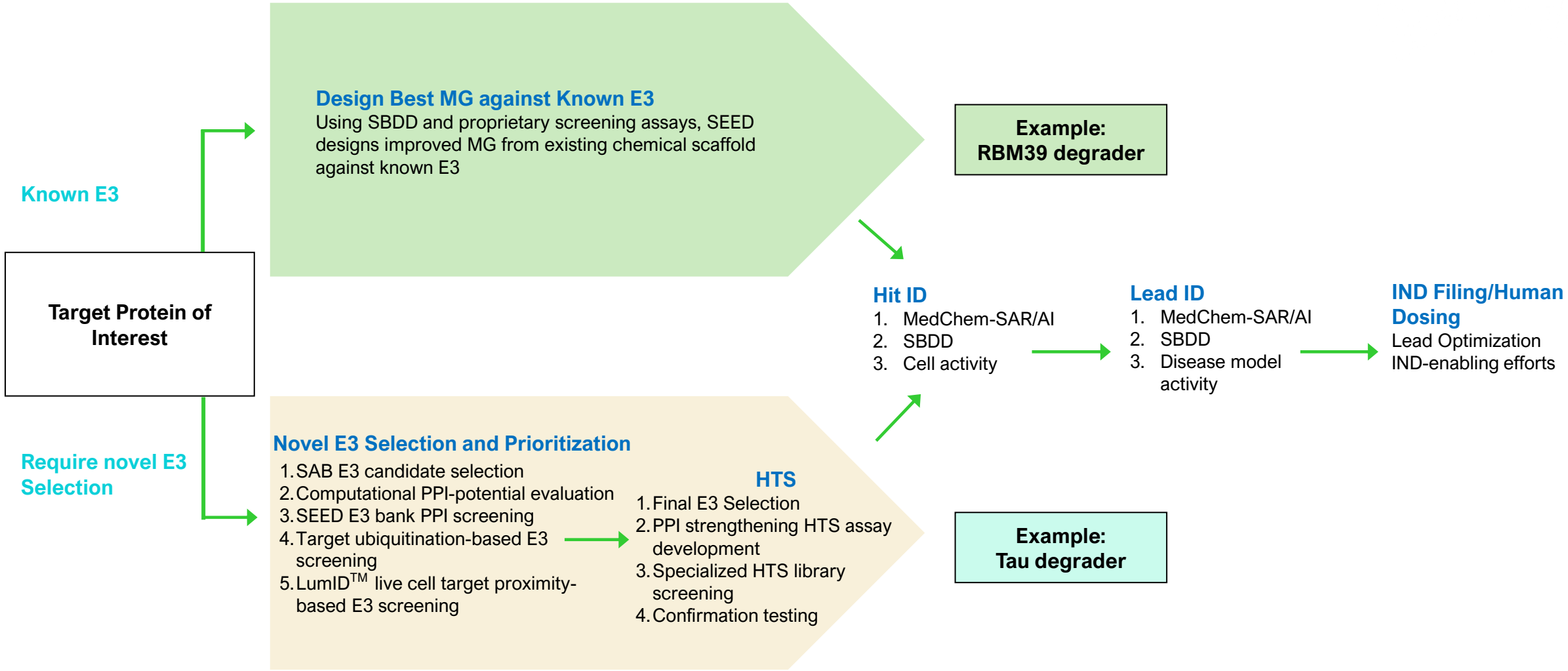


Basal Affinity Validation



POI: Protein of Interest

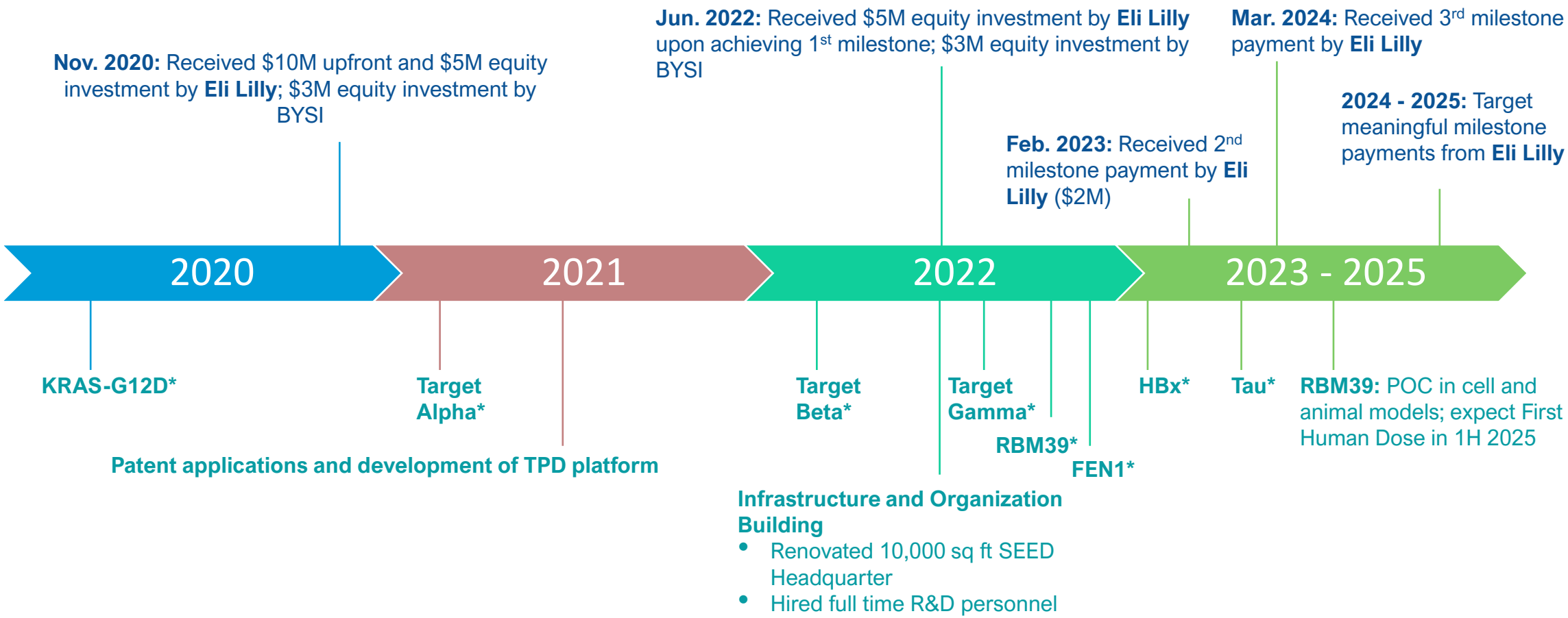
Powerful Two-Pronged Approach Tackling Both Novel and Known E3s



SBDD: Structured-based Drug Design; SAR: Structure Activity Relationship; PPI: Protein-Protein Interactions; HTS: High Throughput Screening

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						1H 2025 FHD
	KRAS-G12D						
	Target Beta						
	FEN1						
Neurodegeneration	Target Alpha						
	Tau						
Immunology	Target Gamma						
Antiviral	HBx						

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

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 **$1.05 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
  - ✓Eli Lilly from Foghorn
  - ✓Sanofi from Kymera
  - ✓GSK from IDEAYA
  - ✓BMS and Orum

- **Clinical stage TPD asset** (early Phase II) has commanded **$650 million** upfront and **$350 million** equity investment in
  - ✓ Pfizer/ Arvinas' collaboration

SEED Differentiation

Target-Centric Approach	Most TPD companies are E3 centric ✓ Majority of SEED's development efforts are target centric, giving SEED unique abilities to go after high value targets
Overcome Key Challenges	How to identify the right E3 for POI? ✓ SEED has unique insights and identified 5 novel E3s for 8 Protein of Interests over 3 years
Highly Effective Translation	World-leading scientific founding team + experienced R&D team → successful and quick translation of breakthrough TPD platform to deep and high value pipeline
Two Pronged Approach	De-risked revenue model: 1) R&D partnership with upfront and milestone payment, and 2) Speedy internal program development to create shareholder value

BeyondSpring

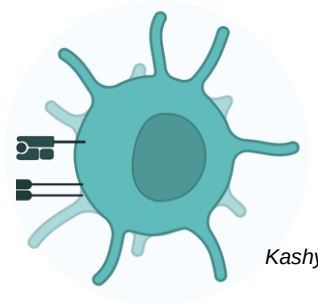
Closing Remarks

Lan Huang, PhD

BeyondSpring Pharmaceuticals, Inc.

BeyondSpring

Plinabulin's effects on DC maturation and reduced chemo-toxicity could partner with RT/Chemo/ADC + PD-1/PD-L1 inhibitor to re-sensitize patients who failed PD-1/PD-L1 inhibitors

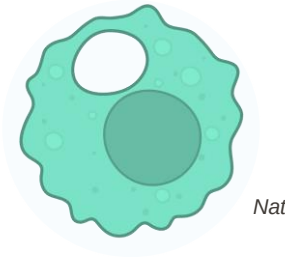


Kashyap, Cell Reports 2019

Dendritic Cells

Plinabulin induces **dendritic cell maturation**

Enhanced antigen presentation and T cell priming



Natoli, Front Oncol 2021

M1-like Macrophages

Plinabulin stimulates **M1-like macrophage polarization and proliferation**

Increased tumor cell killing and cytotoxic T cell recruitment

Huang, PharmacoEconomics 2019
Blayney, JAMA Netw Open 2022
Blayney, JAMA Oncol 2019

Improves Safety*

Plinabulin **reduces chemotherapy-induced neutropenia**

Improved therapeutic index of chemotherapy-based regimens

Collaborates with PD1/PD-L1 targeting agents to enhance T cell function and kill tumor cells

Extends therapeutic duration of potential IO + RT/chemo combinations

Plinabulin Clinical Development

	Indication/Target	Program	Preclinical	Phase 1	Phase 2	Phase 3	Trial Name / Collaborator	
Late stage	**NSCLC (2nd/3rd line)**	Plinabulin + Docetaxel					DUBLIN-3	✓
Late stage	**CIN Prevention**	Plinabulin alone or + Pegfilgrastim					PROTECTIVE-1 & PROTECTIVE-2	✓
Investigator-Initiated Trials	**NSCLC (2nd/3rd line PD-1 failed)**	Plinabulin + Pembrolizumab + Docetaxel					**Study 303**	**Expect Preliminary Data 2H 2024**
Investigator-Initiated Trials	**ES-SCLC (1st line)**	Plinabulin + Pembrolizumab + Etoposide / Platinum					**Study 302**	**Expect Preliminary Data 1H 2025**
Investigator-Initiated Trials	**Multiple cancers (PD-1/PD-L1 failed)**	Plinabulin + PD-1/PD-L1 + Radiation					THE UNIVERSITY OF TEXAS MD Anderson Cancer Center	✓

Summary

Plinabulin: Safety & Efficacy	Lead Asset Plinabulin: >700 cancer patients treated with good tolerability; 2 Positive Phase 3 Studies
Plinabulin Potential	Plinabulin: Potential in re-sensitizing in PD-1/PD-L1 failed patients in multiple cancers, significant unmet needs and treatment limitations
SEED: Novel TPD Platform&Pipeline	SEED: 8 Disclosed Pipeline Assets with 1 oncology asset expected to have first human dose in 1H 2025
Premier Partnerships	SEED: Investment and R&D Collaboration from Eli Lilly
Intellectual Property	Strong Intellectual Property and Technology Protection

Thank You

BeyondSpring