Plinabulin/Docetaxel vs. Docetaxel in 2L/3L NSCLC after Platinum Regimens (DUBLIN-3): a Phase 3 Randomized Controlled Trial

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The EGFR-wild Type 2L/3L NSCLC Has 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 (EGFRwt).
- However, **docetaxel-based therapies (SOC) demonstrate limited efficacy and are associated with >40% severe (grade 3/4) neutropenia.**
- Other approved agents:
  - **Ramucirumab + Docetaxel vs. Docetaxel**: OS HR=0.86, severe neutropenia 49% vs. 40%;[1]
  - **Pemetrexed vs. Docetaxel**: OS HR=0.99, severe neutropenia 5% vs. 40%.[2]
- Additionally, with immunotherapies moving to first line NSCLC, **there is a growing population of 2L/3L patients that are refractory to immunotherapy.**

Attempts to address treatment needs have been challenging

Since Nivolumab's approval 9 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's 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)
6. CARMEN-LC03: Sanofi's tusamitamab ravtansine (ADC)

Recent successful phase 3 studies with mixed results:

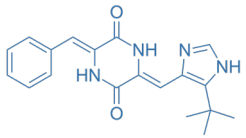
- Lunar (TTfields vs. docetaxel): OS benefit (HR=0.74), but no PFS and ORR benefit
- TROPION-Lung01 (datopotamab deruxtecan - ADC vs. docetaxel): OS did not meet statistical significance in the ITT population, with better OS (HR=0.75) in non-squamous NSCLC.

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

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

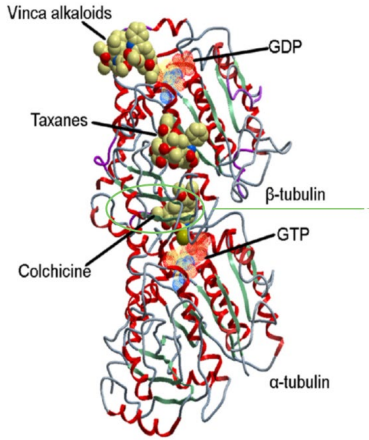
As a Unique Tubulin Binder, Plinabulin Effectively Liberates GEF-H1 from Microtubules Leading to DC Maturation, M1-polarization and T-cell Activation

Plinabulin is a unique tubulin binder[1]

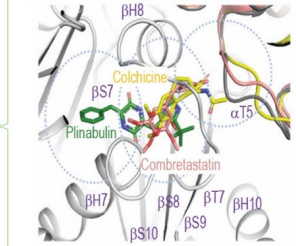


Plinabulin (NPI-2358)

Tubulin Binding Sites



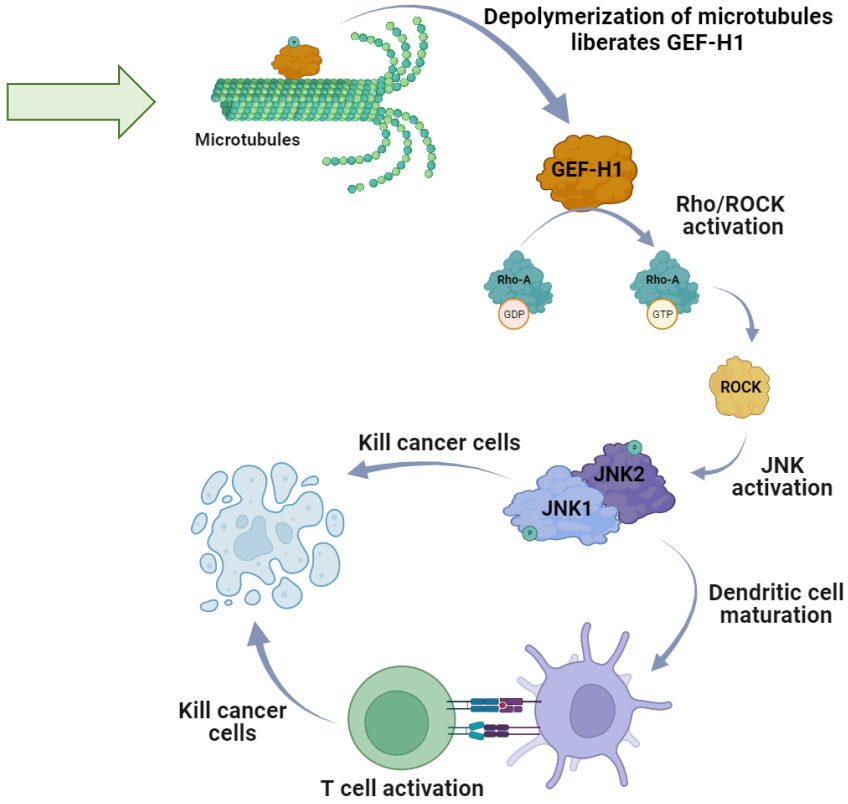
Plinabulin Binds to β-Tubulin, Near the Colchicine Site[1]



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



DC, dendritic cell; GEF-H1, guanine nucleotide exchange factor-H1; JNK, c-Jun N-terminal kinase; ROCK, Rho-associated kinase.

1. La Sala et al. *Chem.* 2021;5:2969–2986; 2. Kashyap et al. *Cell Reports.* 2019;28:3367–3380.

DUBLIN-3 Study Design

Docetaxel + Plinabulin vs. Docetaxel + Placebo in Patients with EGFR Wild-Type 2L/3L NSCLC

Study Plan

- Global, randomized, single-blind (patients only)
- 58 clinical sites (ICON CRO)
- Stratified by region (Asia/non-Asia), prior line (2L or 3L), ECOG (0–1 or 2), prior PD-1/PD-L1 (yes/no)

Primary Endpoint

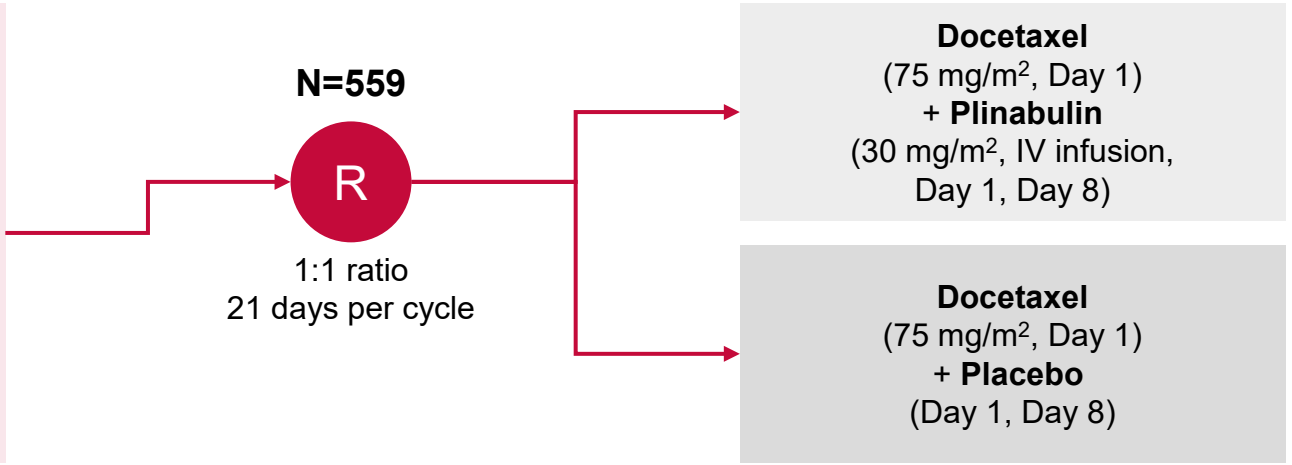
Overall survival (OS)

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 platinum-based treatment regimens
- ≥1 measurable lung lesion
- **Prior checkpoint inhibitor therapy allowed***



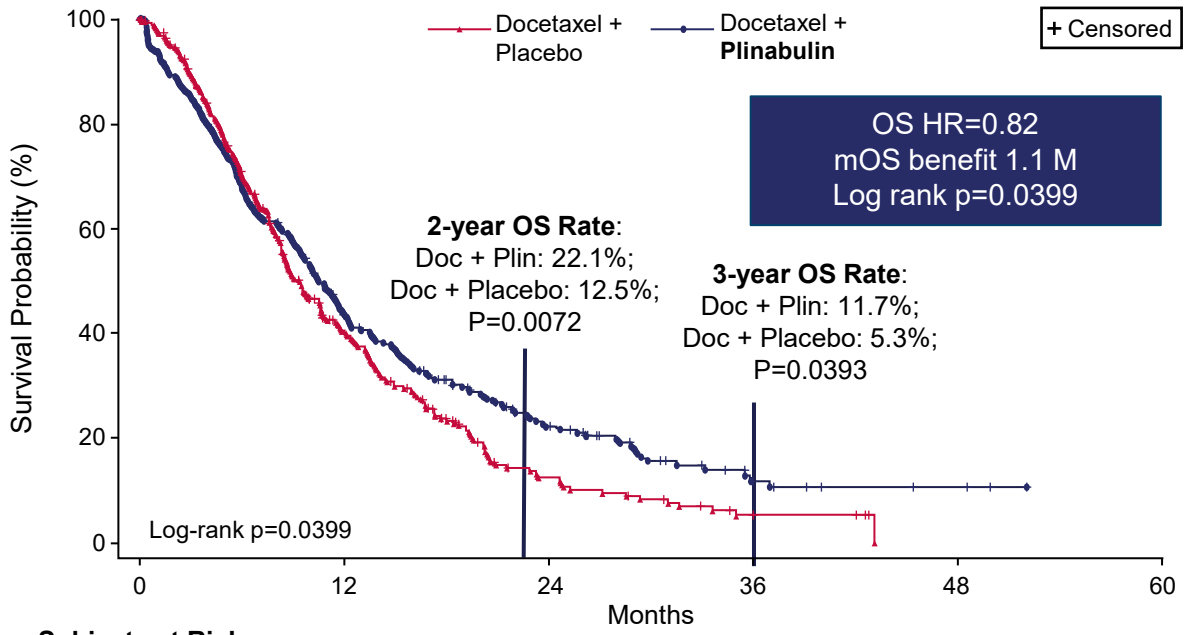
*85% of patients checkpoint inhibitor naïve; 15% failed PD-(L)1 blockade.
2L, second line; 3L, third line; CRO, contract research organization; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival, PFS, progression-free survival; PD-(L)1, programmed death (ligand)-1; QoL, quality of life, Q-TWiST, quality-adjusted time without symptoms or toxicity; R, Randomization.

Baseline Characteristics

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

ECOG, Eastern Cooperative Oncology Group; PD-(L)1, programmed death (ligand)-1.

Plinabulin/Docetaxel Met its Primary Endpoint (OS) with Significant Improvement in Long-term OS Rate



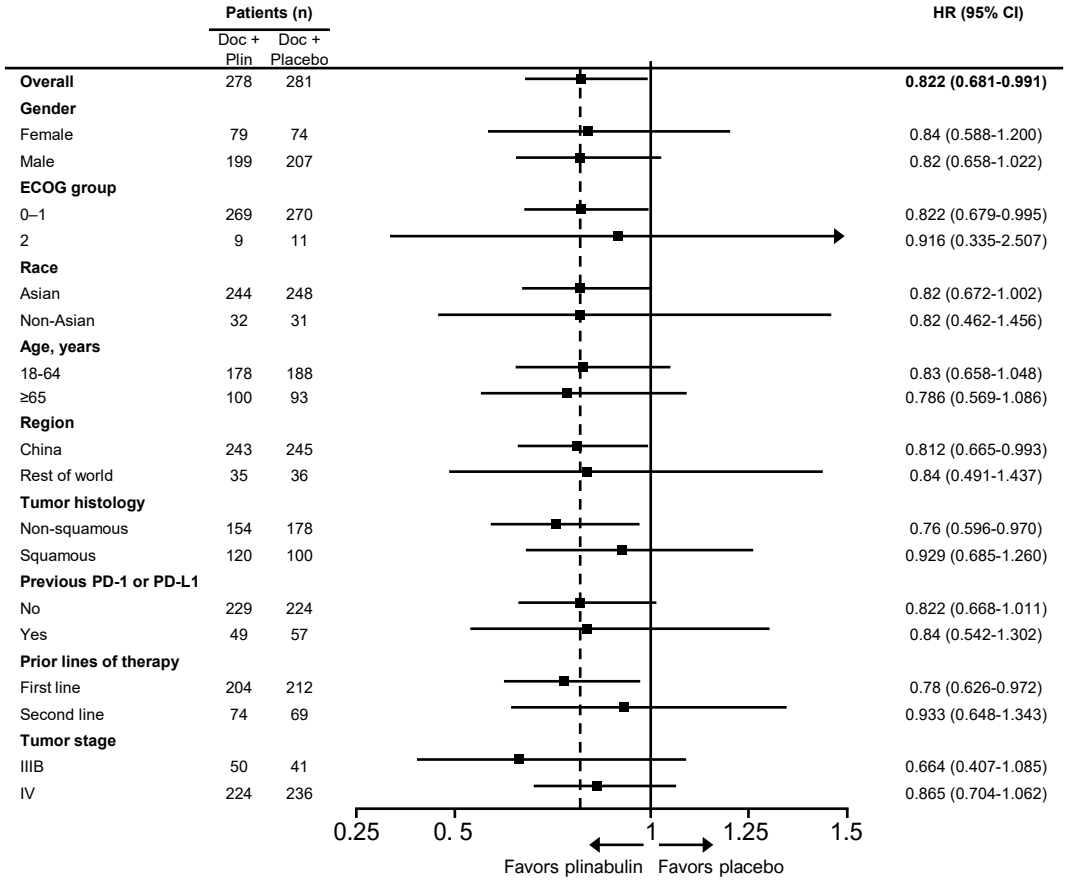
Subjects at Risk

Docetaxel (75mg/m^2) + Placebo					
281	97	21	4	0	0
Docetaxel (75mg/m^2) + Plinabulin (30mg/m^2)					
278	108	41	10	3	0

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

OS Forest Plot-Global, ITT Population

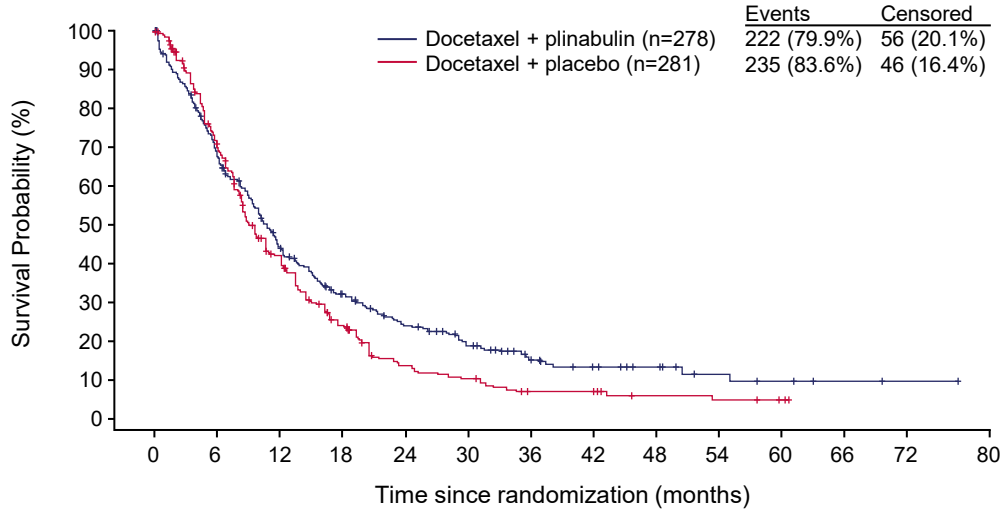
HR<1: Better Efficacy in DP Arm



Doc, docetaxel; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; M, month; mOS, median overall survival; OS, overall survival, PD-(L)1, programmed death (ligand)-1; Plin, plinabulin; SE, standard error.

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

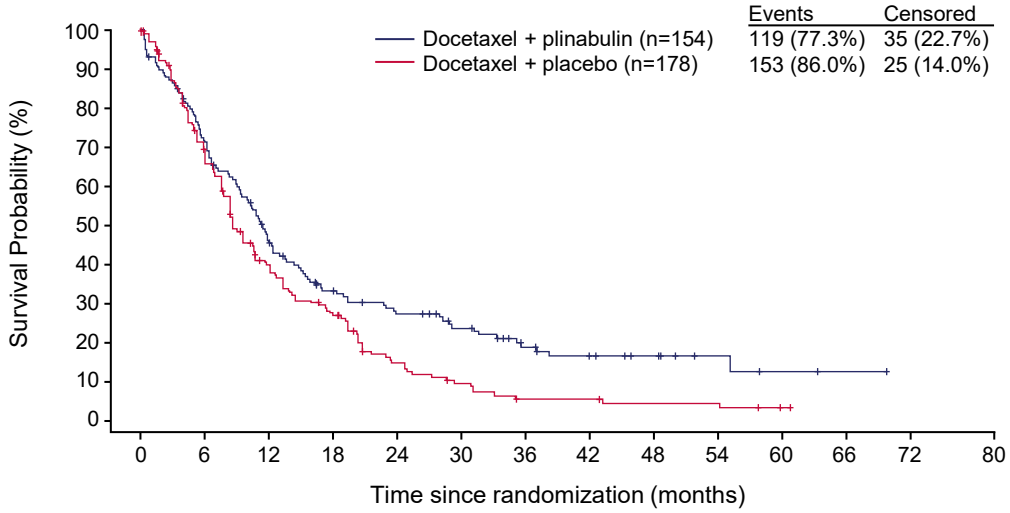
ITT



Number at risk (number censored)

Docetaxel + plinabulin (n=278)	278(0)	182(7)	115(12)	77(20)	54(24)	38(29)	23(38)	16(42)	12(46)	6(51)	4(52)	2(54)	1(55)	0(56)
Docetaxel + placebo (n=281)	281(0)	187(12)	100(22)	55(27)	27(34)	19(35)	10(38)	10(38)	5(42)	4(42)	2(44)	0(46)		

Non-squamous



Number at risk (number censored)

Docetaxel + plinabulin (n=154)	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)	0(0)
Docetaxel + placebo (n=178)	178(0)	115(8)	62(14)	42(15)	20(19)	12(20)	6(21)	6(21)	4(22)	3(22)	1(24)	0(25)		

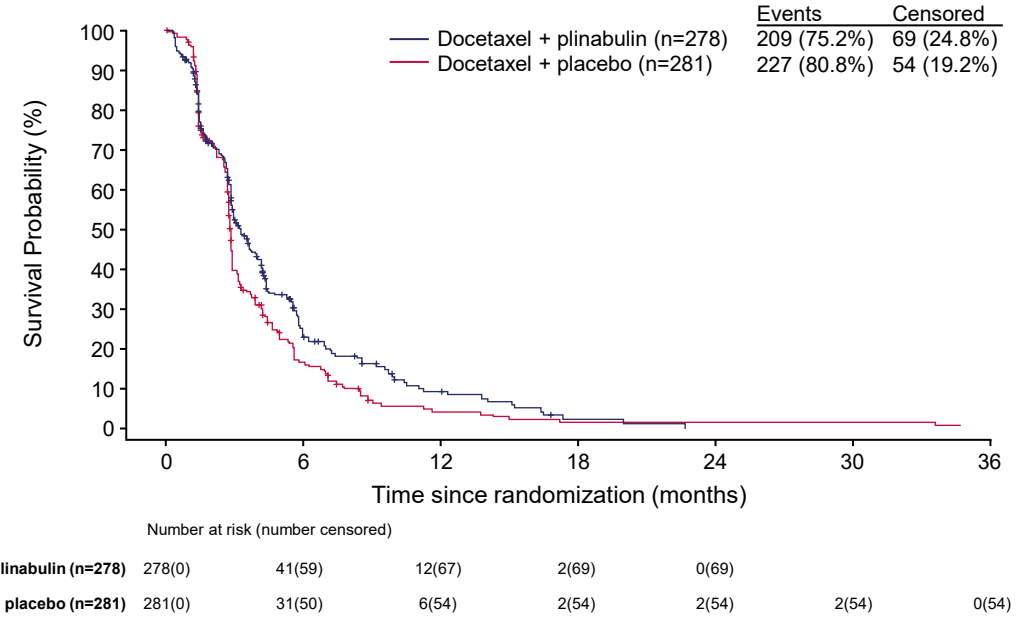
ITT	N	Median OS (95% CI)	HR (95% CI)	Log rank P value
Docetaxel	281	9.3 (8.35, 10.65)		
Plinabulin + Docetaxel	278	10.8 (9.37, 11.97)	**0.81 (0.68, 0.98)**	**P = 0.0270**

Non-squamous	N	Median OS (95% CI)	HR (95% CI)	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**

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival.

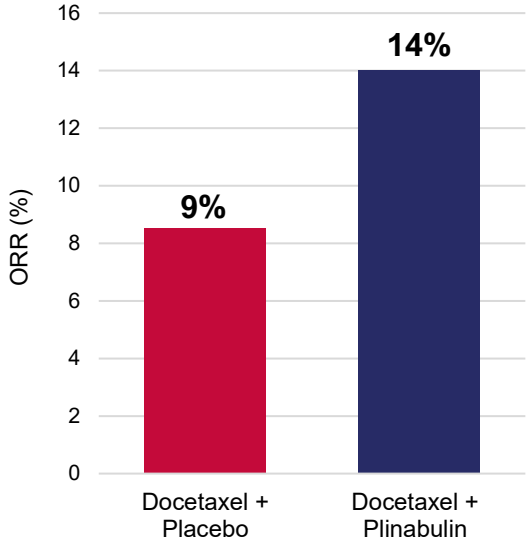
Dublin-3 Met All Key Secondary Endpoints

PFS



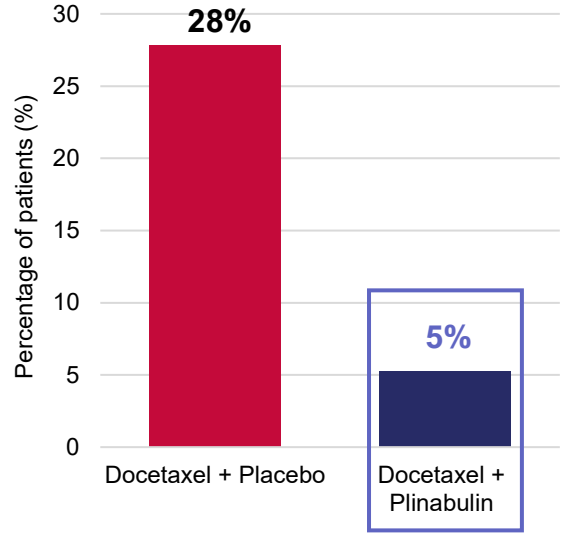
ITT	N	Median PFS Month (95% CI)	HR (95% CI)	Log rank P value
Docetaxel	281	2.8 (2.76, 2.93)		
Plinabulin + Docetaxel	278	3.3 (2.89, 3.88)	**0.79 (0.66, 0.96)**	**P = 0.0174**

ORR (CR+PR)



P value = 0.0404

Grade 4 Neutropenia
(Cycle 1, Day 8)

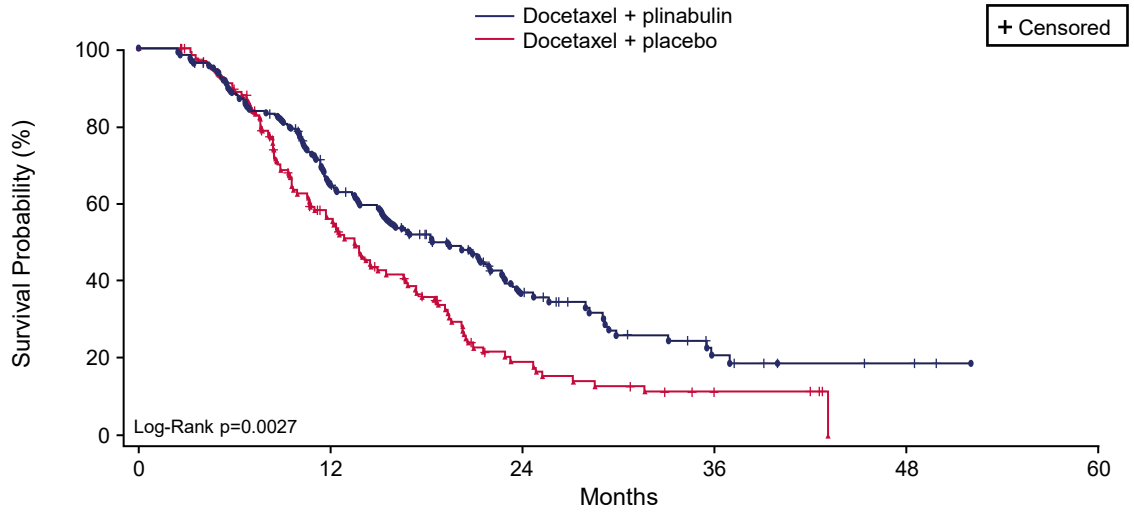


P value <0.0001

CI, confidence interval; CR, complete response; HR, hazard ratio; ITT, intention-to-treat; ORR, overall response rate; PFS, progression-free survival; PR, partial response.

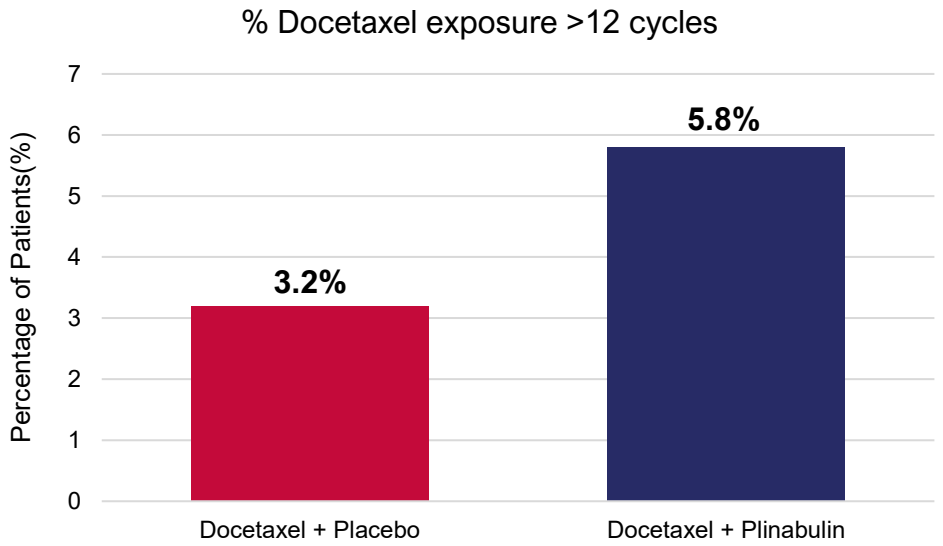
Improved OS Benefit with More Cycles of Treatment; Plinabulin Increases Cycles of Treatment

OS K-M graph: Patients who received ≥4 treatment cycles of docetaxel/plinabulin



	N	Median OS	HR	P value
Docetaxel	127	13.5 (10.98, 16.54)		
Plinabulin + Docetaxel	133	18.3 (14.96, 22.88)	**0.639**	**P = 0.0027**

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



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

HR, hazard ratio; K-M, Kaplan-Meier; OS, overall survival.

DUBLIN-3: Treatment Related Adverse Events

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

TEAE, treatment emergent adverse event; WBC, white blood cell.

Plinabulin/Docetaxel with Durable Anti-cancer Benefit as a Potential Practice-changing Treatment for 2L/3L NSCLC with No Driver Mutation

The addition of Plinabulin as a single agent added to SOC Docetaxel led to improved anti-cancer efficacy, in terms of OS, PFS and ORR; and enhanced safety in reducing docetaxel-induced severe neutropenia.

Efficacy

- Significant survival benefit in ITT (OS HR=0.82).
  - Doubled 2-year, 3-year survival rate; robust OS data with OS HR<1 in all sub-group analyses; same HR for Asian and non-Asian patients.
- Significant PFS and ORR benefit.
- Additional 24 months follow up after database lock showed sustained OS benefit (OS HR=0.81), with more pronounced benefit in non-squamous population (OS HR=0.72).

Safety and Tolerability

- The regimen was well tolerated with similar TEAE rate and lower Grade 4 TEAE rate.
- Side effects included transient hypertension, which resolved in 4–6 hours, nausea, vomiting and GI side effects.
- Docetaxel-induced neutropenia was significantly reduced, allowing increased treatment exposure.

2L, second line; 3L, third line; DoR, duration of response; GI, gastrointestinal; HR, hazard ratio; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival, PFS, progression-free survival; SOC, standard of care; TEAE, treatment-emergent adverse events.

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