THE LANCET
Respiratory Medicine

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Han B, Feinstein T, Shi Y, et al. Plinabulin plus docetaxel versus docetaxel in patients with non-small-cell lung cancer after disease progression on platinum-based regimen (DUBLIN-3): a phase 3, international, multicentre, single-blind, parallel group, randomised controlled trial. *Lancet Respir Med* 2024; published online Sept 9. https://doi.org/10.1016/S2213-2600(24)00178-4.

Appendix

Supplementary Methods

1.0 Inclusion criteria

Patients with non-squamous or squamous NSCLC who have progressed after treatment with one or two, non-docetaxel-containing systemic therapy regimen(s) for advanced or metastatic disease and with at least one measurable lung lesion; patients might also have had failed prior immunotherapy with a PD-1/PD-L1 inhibitor. One prior treatment regimen must be a platinum-based regimen.

The patients must satisfy all of the following inclusion/exclusion criteria in order to be eligible for the study:

1. Males and females ≥18 years of age.

2. ECOG performance status ≤2.

3. Histopathologically or cytologically confirmed non-squamous or squamous non-small cell lung cancer (NSCLC).

4. Disease progression during or after treatment with one or two treatment regimen(s). Treatment regimens can be chemotherapy, targeted therapy, biological therapy, or immunotherapy for advanced (Stage IIIB) or metastatic disease (Stage IV). Modification of a regimen to manage toxicity with a different drug does not constitute a new regimen. Maintenance therapy following platinum-based chemotherapy is not considered as a separate regimen. Adjuvant or neoadjuvant chemotherapy and/or chemo-radiation for early-stage disease do not count as prior systemic therapy. Prior radiation therapy is not exclusionary. Prior immunotherapy with a PD-1/PD-L1 inhibitor is not exclusionary. Prior treatment for advanced or metastatic disease must have included a platinum-based regimen. (Treatment of early-stage disease [Stage IIIA or earlier] with a platinum-containing therapy does not count).

5. Patients with active brain metastasis or leptomeningeal involvement with brain metastases who are asymptomatic, and whose lesions by imaging are at least stable and without interim development of new lesions for at least 4 weeks may be enrolled. Patients who require continued therapy with steroid medication for management for their brain metastases are eligible; dosing must be stable for at least 4 weeks prior to randomization.

6. Patients must have at least one measurable lung lesion of ≥10 mm by CT or MRI per RECIST 1.1 criteria. Radiographic tumor assessment is to be performed within 28 days prior to randomization.

7. All patients with non-squamous NSCLC must have been tested for 19 deletion and exon 21 L858R substitution mutation. Only patients without EGFR sensitizing mutations are eligible, and they must have progressed on platinum-based chemotherapy. Patients with known ALK-rearrangements should be treated with an appropriate tyrosine kinase inhibitor (TKI) before entering the study. The TKI regimen would count as a line of treatment.

8. All adverse events of any prior systemic therapy, surgery, or radiotherapy, must have resolved to CTCAE (v4.03) Grade ≤2, except for neurological adverse events that must have resolved to Grade ≤1.

9. The following laboratory results from the central laboratory within 14 days prior to Cycle 1 Day 1 study drug administration:

• Hemoglobin ≥9 g/dL independent of transfusion or growth factor support;

• Absolute neutrophil count ≥1.5 x 109/L independent of growth factor support;

• Platelet count ≥100 x 109/L independent of transfusion or growth factor support;

• Serum total bilirubin ≤ ULN, unless the patient has a diagnosis of Gilbert's disease in which case serum bilirubin ≤3.0 times ULN;

• AST and ALT ≤2.5 x ULN (≤1.5 x ULN if alkaline phosphatase is >2.5 x ULN);

• Serum creatinine ≤1.5 x ULN;

10. Life expectancy more than 12 weeks.

11. Female patients of childbearing potential have a negative pregnancy test at baseline. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression.

a. Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug.

b. Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner.

c. For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 11b above during the treatment period and for at least 3 months after the last dose of study drug.

12. Signed informed consent.

2.0 Exclusion Criteria

Patients with any of the following will be excluded from participation in the study.

1. Administration of chemotherapy, immunotherapy, biological, targeted, or radiation therapy or investigational agent (therapeutic or diagnostic) within 3 weeks prior to receipt of study medication. Major surgery, other than diagnostic surgery, within 4 weeks before first study drug administration.

2. Significant cardiac history:

• History of myocardial infarction or ischemic heart disease within 1 year (within a window of 18 days) before first study drug administration;

• Uncontrolled arrhythmia;

• History of congenital QT prolongation;

• ECG findings consistent with active ischemic heart disease;

• New York Heart Association Class III or IV cardiac disease;

• Uncontrolled hypertension: blood pressure consistently greater than 150 mm Hg systolic and 100 mm Hg diastolic in spite of antihypertensive medication.

3. Patients who have received prior treatment with docetaxel.

4. Prior transient ischemic attack or cerebrovascular accident within the past year (within an 18-day window). Any neurologic toxicities ≥ Grade 2 within 3 weeks of randomization.

5. History of hemorrhagic diarrhea, inflammatory bowel disease or active uncontrolled peptic ulcer disease. (Concomitant therapy with ranitidine or its equivalent and/or omeprazole or its equivalent is acceptable). History of ileus or other significant gastrointestinal disorder known to predispose to ileus or chronic bowel hypomotility.

6. Active uncontrolled bacterial, viral, or fungal infection requiring systemic therapy.

7. Known infection with human immunodeficiency virus (HIV) or active hepatitis A, B, or C.

8. Known prior hypersensitivity reaction to any product containing polysorbate 80, polyoxyethylene 15 hydroxystearate/Macrogol 15 hydroxystearate (Solutol HS 15/ Kolliphor HS 15).

9. Female subject who is pregnant or lactating.

10. Second malignancy unless in remission for >5 years. (Non-melanoma skin cancer or carcinoma in situ of the cervix treated with curative intent is not exclusionary).

11. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient. Examples of such conditions include uncontrolled diabetes, infection requiring parenteral anti-infective treatment, liver failure, any altered mental status or any psychiatric condition that would interfere with the understanding of the informed consent form.

12. Unwilling or unable to comply with procedures required in this protocol.

3.0 Q-TWiST analysis

A Q-TWiST analysis was conducted by analyzing survival data (PFS and OS) in combination with the AEs of Grade ≥3 and the EORTC QLQ-C30 data to assess the differences between groups.

The Q-TWiST methodology partitioned patients' survival into 3 categories:

1. Toxicity (TOX): time with AE Grade ≥3 after randomization and before disease progression. Patients with no AE Grade ≥3 were assigned a zero TOX time.
2. Time without symptoms or toxicities (TWiST): time from randomization to disease progression without Grade ≥3 AEs. The TWiST time was defined as the PFS time minus the TOX time. Patients who were alive and had no disease progression or who were lost to follow-up were censored at the time of the last tumor assessment.
3. Relapse (REL): time from disease progression to death.
   The relapse time was defined as the OS time minus the PFS time. Patients who were alive or who were lost to follow-up were censored at the time of the last contact.

The survival curves associated with TOX, PFS, and OS, were estimated with the Kaplan-Meier method. The restricted mean duration of each health state was derived from the area under the Kaplan-Meier curve. The mean duration of TWiST and REL were calculated as follows:

- TWiST = PFS–TOX
- REL = OS–PFS

The mean Q-TWiST was calculated as follows:

- Q-TWiST = U_{TOX} × TOX + U_{TWiST} × TWiST + U_{REL} × REL

Where U_{TOX}, U_{TWiST}, and U_{REL} represents the EQ-5D utility weights for each of the 3 health states.

The utility weights were derived using a mapping algorithm of the EORTC QLQ-C30 score onto the EQ-5D 5 dimensions then converted into utilities using the U.S. utility weights. The mean and mean difference in Q-TWiST for each treatment group were calculated. The 95% CIs for the mean difference and the p-values were calculated using a t-test based on the normal approximation, with the variance estimated using the bootstrap method. Two time horizons were analyzed. The primary

analysis was restricted to the median overall follow-up time. A sensitivity analysis was conducted using the longest survival follow-up time.

Supplementary Table 1. Baseline characteristics for non-squamous patients

	Docetaxel + Placebo n=178	Docetaxel + Plinabulin n=154
Median age, y (range)	59 (28, 85)	60 (37, 82)
Sex, n (%)		
Male	118 (66·3)	95 (61·7)
Female	60 (33·7)	59 (38·3)
Tumor histology, n (%)		
Non-squamous	178 (100)	154 (100)
Squamous	0	0
Missing	0	0
ECOG, n (%)		
0	29 (16·3)	23 (14·9)
1	142 (79·8)	127 (82·5)
2	7 (3·9)	4 (2·6)
Regional distribution, n (%)		
Asian	146 (82·0)	132 (85·7)
Western	32 (18·0)	22 (14·3)
Previous treatment, n (%)		
First-line	134 (75·3)	113 (73·4)
Second-line	44 (24·7)	41 (26·6)
Previous radiotherapy, n (%)		
Yes	49 (27·5)	42 (27·3)
No	129 (72·5)	112 (72·7)
Previous surgery, n (%)		
Yes	91 (51·1)	74 (48·1)
No	87 (48·9)	80 (51·9)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; n = number of patients.

Supplementary Table 2. Baseline characteristics for patients on second-line therapy

	Docetaxel + Placebo n=212	Docetaxel + Plinabulin n=204
Median age, y (range)	60·5 (25, 85)	61·0 (37, 82)
Sex, n (%)		
Male	157 (74·1)	148 (72·5)
Female	55 (25·9)	56 (27·5)
Tumor histology, n (%)		
Non-squamous	134 (63·2)	113 (55·4)
Squamous	75 (35·4)	87 (42·6)
Missing	3 (1·4)	4 (2·0)
ECOG, n (%)		
0	30 (14·2)	28 (13·7)
1	176 (83·0)	171 (83·8)
2	5 (2·4)	5 (2·5)
Missing	1 (0·5)	0
Regional distribution, n (%)		
Asian	195 (92·0)	189 (92·6)
Western	17 (8·0)	15 (7·4)
Previous treatment, n (%)		
First-line	212 (100·0)	204 (100·0)
Previous platinum treatment, n (%)		
Yes	212 (100·0)	204 (100·0)
Previous radiotherapy, n (%)		
Yes	50 (23·6)	54 (26·5)
No	162 (76·4)	150 (73·5)
Previous surgery, n (%)		
Yes	100 (47·2)	85 (41·7)
No	112 (52·8)	119 (58·3)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; n = number of patients.

Supplementary Table 3. Objective response rate: Investigator Assessments – ITT Population

	Docetaxel + Placebo n=281	Docetaxel + Plinabulin n=278
ORR (CR+PR), n/N (%)	19/281 (6·76)	34/278 (12·23)
Difference		
DP Arm-D Arm (%)	5·47	
95% CI	(0·63, 10·31)	
P-value	0·0275	

Abbreviations: CI = confidence interval; CMH = Cochran–Mantel–Haenszel; CR = complete response; D, docetaxel; DP, docetaxel and plinabulin; ITT = intent to treat; n = number of patients; ORR = objective response rate; PR = partial response.

P-value was calculated by using CMH test. The CI was constructed based on normal approximation.

Supplementary Table 4. Progression-free survival: Investigator assessments – ITT population

	Docetaxel + Placebo n=281	Docetaxel + Plinabulin n=278
Number of subjects	**281**	**278**
Censored[1], n (%)	67 (23·84)	91 (32·73%)
Death, n (%)	214 (76·16)	187 (67·27%)
K-M estimate of progression-free survival [2] (months)		
25th percentile (95% CI)	1·5 (1·48, 1·74)	1·8 (1·48, 2·50)
Median (95% CI)	3·0 (2·83, 3·71)	3·6 (2·96, 4·40)
75th percentile (95% CI)	5·6 (4·67, 5·88)	7·0 (5·95, 10·42)
Min, max	0·03, 35·01	0·03, 28·83
P-value (log-rank test, 2-sided)		0·0082
Hazard ratio[3] (95%CI)		0·765 (0·628, 0·933)
P-value (standardized score process test)[4]		0·0600
RMST (months) (SE)	4·4 (0·329)	5·95 (0·445)
P-value (RMST Test of Equality)		0·0062

Abbreviations: CI = confidence interval; ITT = intent-to-treat; K-M = Kaplan-Meier; Max = maximum; Min = minimum; n = number of patients; PFS = progression-free survival; RMST = restricted mean survival time; SE = standard error.

[1] Patients without a documented disease progression or death were censored according to rules in SAP 6.3.2.3.

[2] PFS time was calculated as the number of months from randomization date to progression or death or date of censoring.

[3] The point estimate and corresponding 95% CI for the hazard ratio were calculated via Cox proportional hazards model with the treatment group used as the only covariate.

[4] Standardized score process test was used to assess the assumption of proportional hazards.

Supplementary Table 5. Grade 4 neutropenia on Cycle 1 Day 8 and all cycles Day 8 in the ITT population

Grade 4 neutropenia	Docetaxel + Plinabulin n/N (%)	Docetaxel + Placebo n/N (%)	Treatment difference % (95% CI)	p-value
Cycle 1, Day 8	12/228 (5·26)	67/241 (27·80)	-22·54 (-28·89, -16·18)	P<0·0001
All cycles, Day 8	14/273 (5·13)	92/274 (33·58)	-28·45 (-34·62, -22·27)	P<0·0001

Abbreviations: CI = confidence interval; ITT = intent-to-treat; n/N = number of patients.

Supplementary Table 6. Grade 4 neutropenia in subgroups on Cycle 1 Day 8

Grade 4 neutropenia	Docetaxel + Plinabulin n/N (%)	Docetaxel + Placebo n/N (%)	Treatment difference % (95% CI)	p-value
Non-squamous histopathology	5/148 (3·38)	44/174 (25·29)	-21·91 (28·99, -14·88)	P<0·0001
Previous treatment				
First-line	6/169 (3·55)	49/179 (27·37)	-23·82 (-30·93, -16·72)	P<0·0001
Second-line	6/59 (10·17%)	18/62 (29·03%)	-18·86 (-32·54, -5·18)	P=0·0096

Abbreviations: CI = confidence interval; n/N = number of patients.

Supplementary Table 7. G-CSF use in each treatment cycle

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

Abbreviations: G-CSF = granulocyte-colony stimulating factor; n/N = number of patients.

Supplementary Table 8. Median OS related to plinabulin/docetaxel treatment cycle

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

Abbreviations: CI = confidence interval; HR = hazard ratio; M = month; n = number of patients; NA = not applicable; OS = overall survival.

Supplementary Table 9. Docetaxel exposure

	Statistical Description	Global	
		Docetaxel + Plinabulin	**Docetaxel + Placebo**
Exposure duration (weeks)	n	274	278
	Mean (SD)	11·12 (12·67)	9·47 (9·61)
	Median (IQR: Q1, Q3)	8·22 (3·14, 15·57)	6·43 (3·14, 13·57)
	Range (min, max)	0·14, 72·29	0·14, 69·71
Total Dosage (mg)	n	274	277
	Mean (SD)	534·68 (460·06)	488·88 (373·97)
	Median (IQR: Q1, Q3)	413·65 (236·0, 660·0)	390 (253·0, 621·7)
	Range (min, max)	100, 2816	15, 2848

Abbreviations: IQR = interquartile range; max = maximum; min = minimum; n = number of patients; SD = standard deviation.

Supplementary Table 10. Summary of Grade 3 or 4 exposure-adjusted event rates

	Grade 3 or 4 Event Rates Adjusted by Exposure		Grade 4 Only Event Rates Adjusted by Exposure	
	Docetaxel + Plinabulin n=274	**Docetaxel + Placebo n=278**	**Docetaxel + Plinabulin n=274**	**Docetaxel + Placebo n=278**
Descriptive Statistics				
Number of patients with events, n (%)	203 (74·1)	212 (76·3)	61 (22·3)	121 (43·5)
Total number of years	83·43	71·65	83·43	71·65
Total number of events	814	783	141	221
Observed event rate per year	9·76	10·93	1·69	3·08
Estimated event rate per year (95% CI)	9·76 (9·11, 10·45)	10·93 (10·19, 11·72)	1·69 (1·43, 1·99)	3·08 (2·70, 3·52)
Treatment Difference				
RR vs Docetaxel + Placebo (95% CI)	0·89 (0·81, 0·98)		0·55 (0·44, 0·68)	
P-value vs· Docetaxel + Placebo	0·0235		<0·0001	

Abbreviations: CI = confidence interval; n = number of patients; RR = rate ratio.

Supplementary Table 11. Summary of treatment after end of study in the safety population

Treatment	Docetaxel + Placebo (N=278)	Docetaxel + Plinabulin (N=274)
Targeted therapy (TKI)	76 (27·3)	56 (20·4)
Radiation	13 (4·7)	13 (4·7)
Chemotherapy	47 (16·9)	42 (15·3)
Chinese medicine treatment	11 (4·0)	9 (3·3)
Unknown	10 (3·6)	12 (4·4)
PD-1/PD-L1	17 (6·1)	24 (8·8)

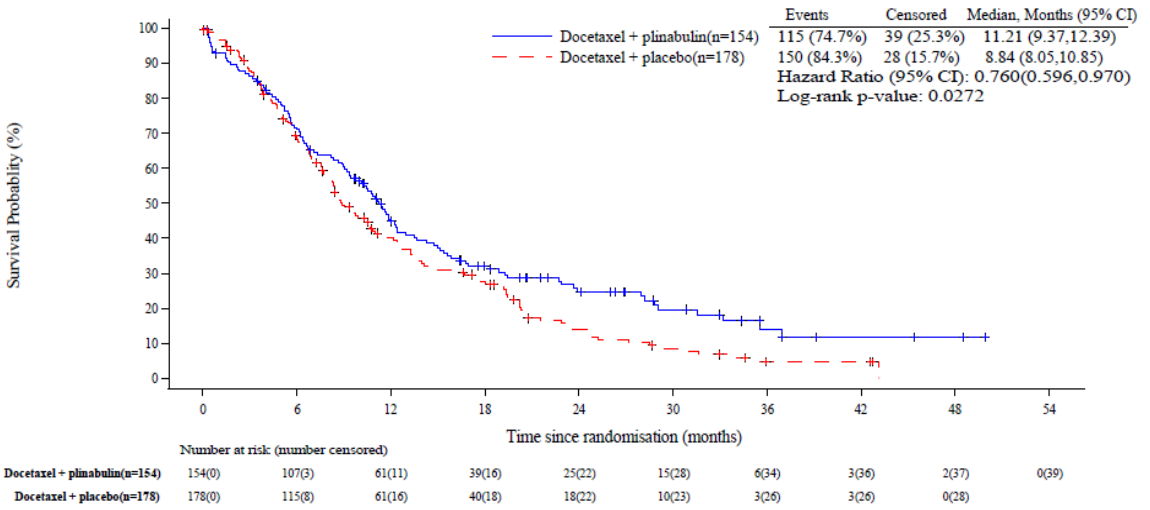
Abbreviations: PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand 1; TKI = tyrosine kinase inhibitor.

Supplementary Table 12. Overall Summary of Treatment-Emergent Adverse Events – Safety Population

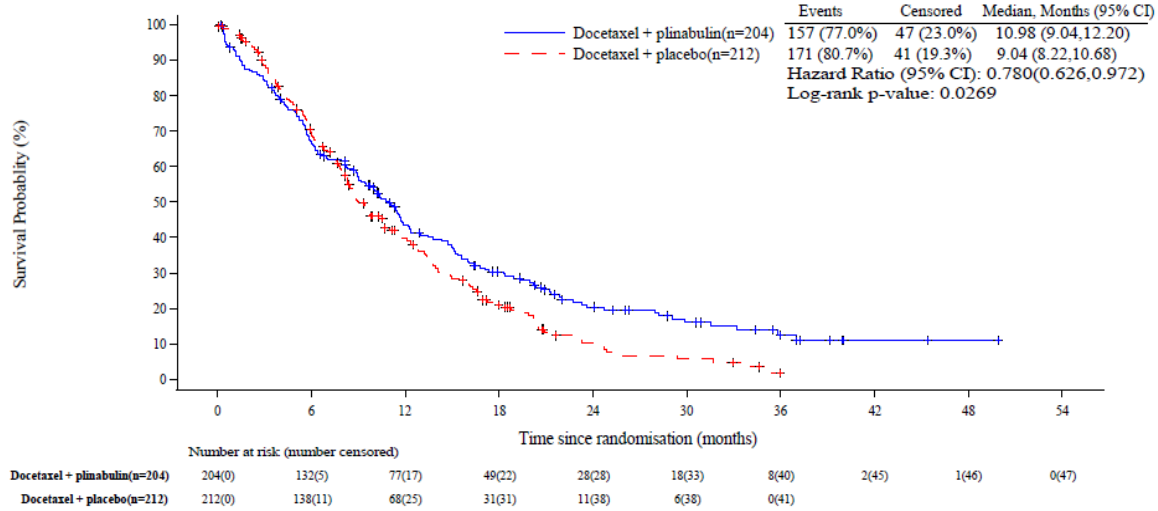
	Docetaxel 75 mg/m^2 + Placebo (N=278) n (%)	Docetaxel 75 mg/m^2 + Plinabulin 30 mg/m^2 (N=274) n (%)
Any TEAE	**276 (99.3)**	**273 (99.6)**
Grade 1	13 (4.7)	12 (4.4)
Grade 2	49 (17.6)	56 (20.4)
Grade 3	85 (30.6)	141 (51.5)
Grade 4	119 (42.8)	52 (19.0)
Grade 5 (death)	10 (3.6)	12 (4.4)
Serious	92 (33.1)	115 (42.0)
Leading to death	10 (3.6)	12 (4.4)
Leading to docetaxel modification	108 (38.8)	135 (49.3)
Leading to plinabulin modification	0	164 (59.9)
Leading to permanent discontinuation of docetaxel	30 (10.8)	34 (12.4)
Leading to permanent discontinuation of plinabulin	0	34 (12.4)

Abbreviations: n/N = number of patients; TEAE = treatment-emergent adverse event.

A



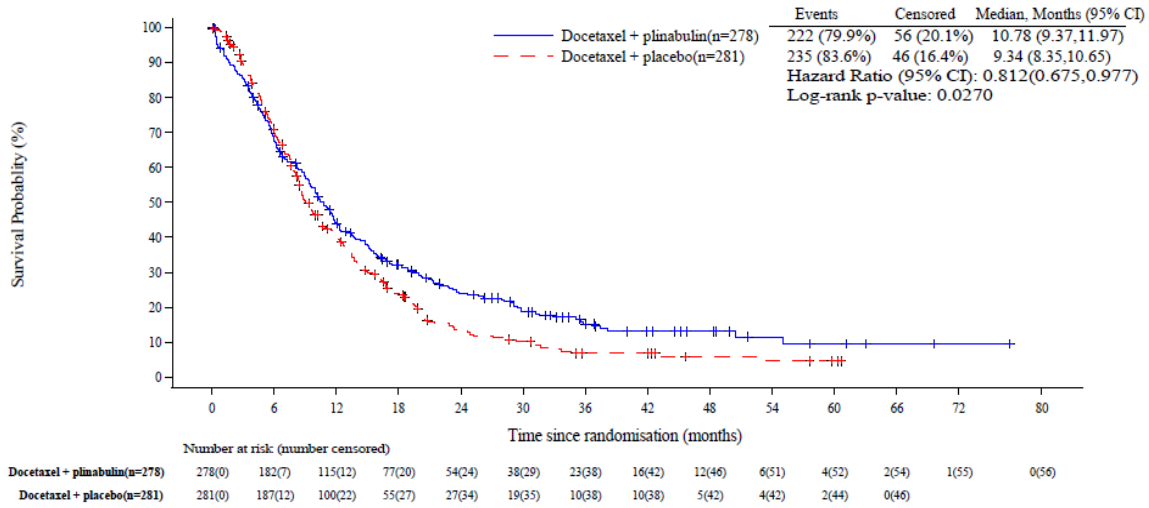
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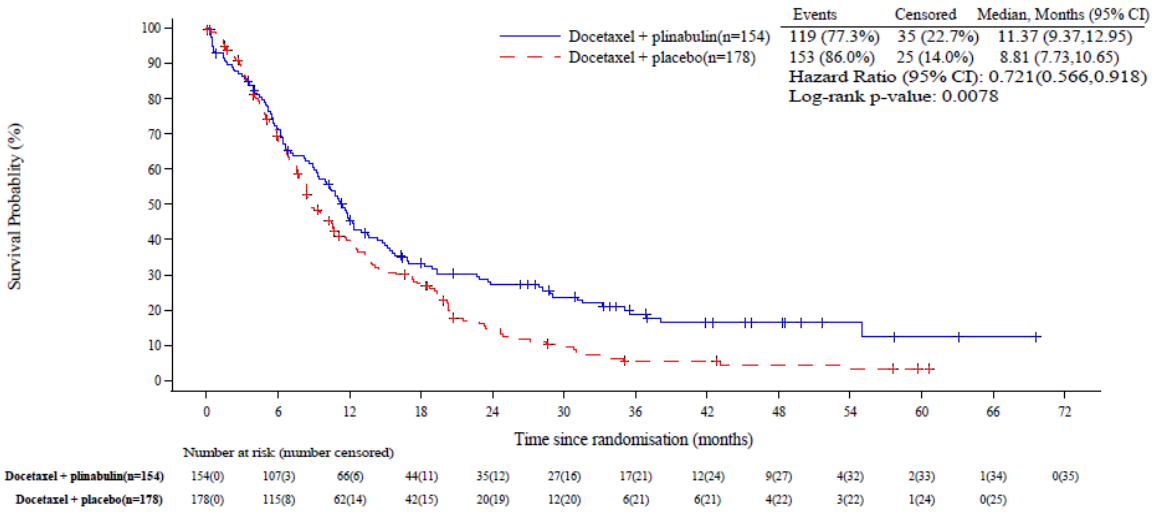
Supplementary Figure 1. Kaplan-Meier plot of overall survival in the non-squamous population (A) and the second-line population (B)

Abbreviations: CI = confidence interval; D = docetaxel and placebo; DP = docetaxel and plinabulin; HR = hazard ratio; n = number of patients.

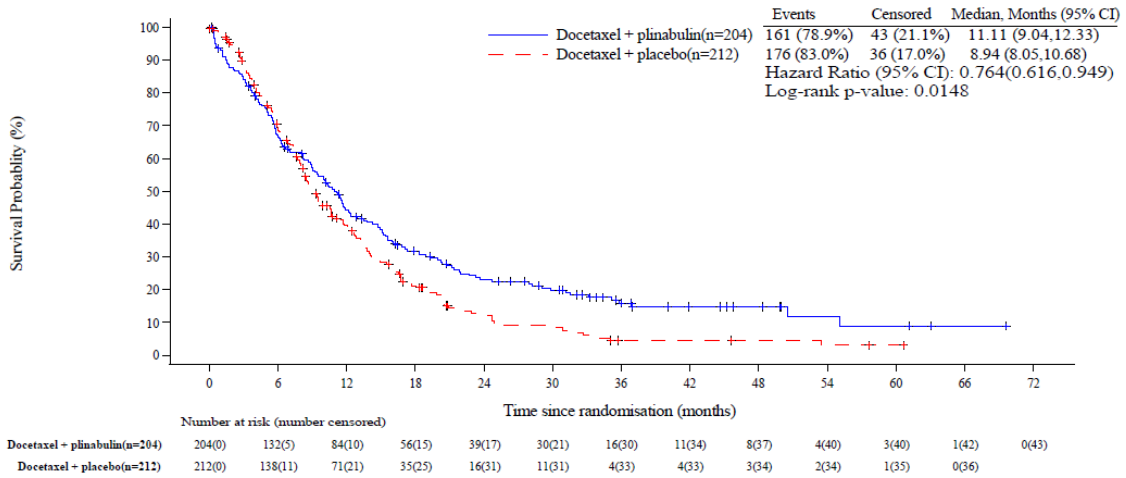
A


Events Censored Median, Months (95% CI)
Docetaxel + plinabulin(n=278) 222 (79.9%) 56 (20.1%) 10.78 (9.37,11.97)
Docetaxel + placebo(n=281) 235 (83.6%) 46 (16.4%) 9.34 (8.35,10.65)
Hazard Ratio (95% CI): 0.812(0.675,0.977)
Log-rank p-value: 0.0270
Survival Probability (%)
Time since randomisation (months)
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)

B

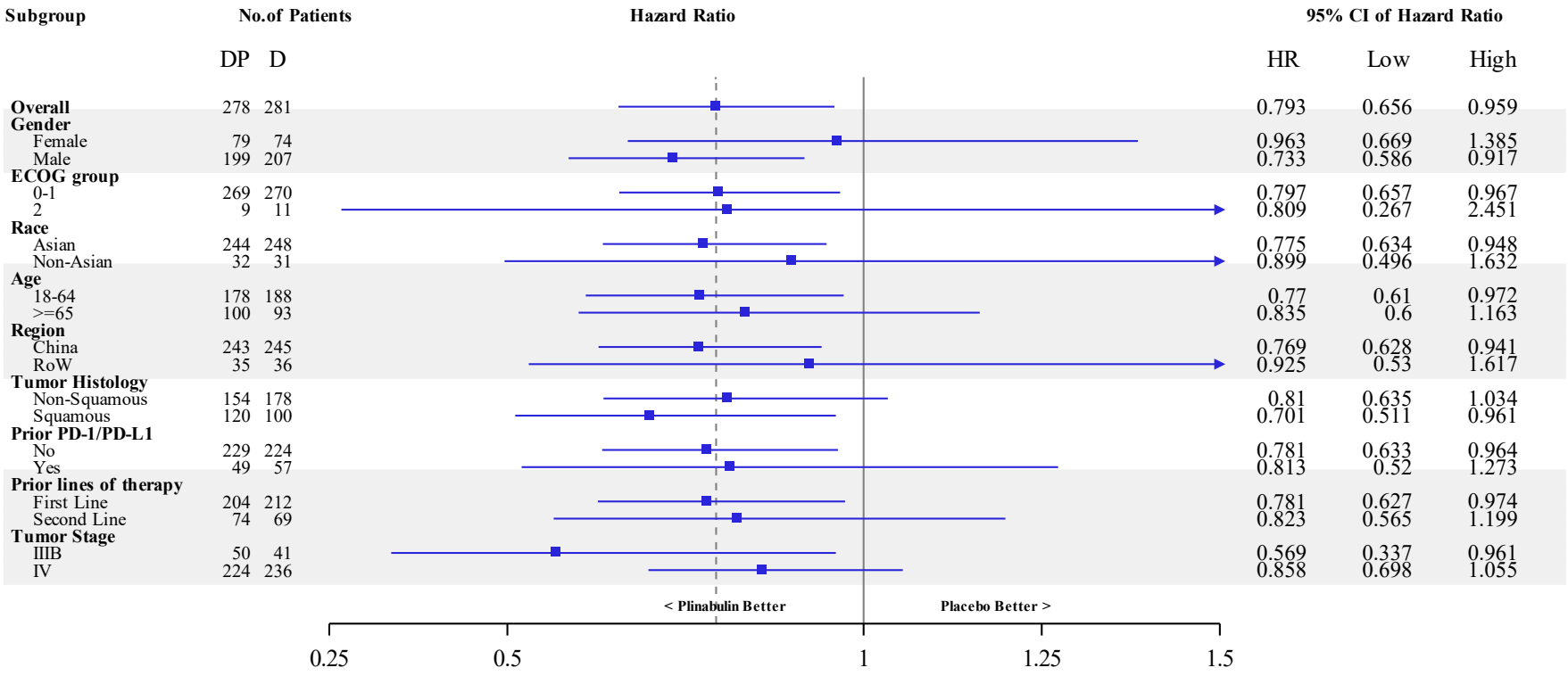

Events Censored Median, Months (95% CI)
Docetaxel + plinabulin(n=154) 119 (77.3%) 35 (22.7%) 11.37 (9.37,12.95)
Docetaxel + placebo(n=178) 153 (86.0%) 25 (14.0%) 8.81 (7.73,10.65)
Hazard Ratio (95% CI): 0.721(0.566,0.918)
Log-rank p-value: 0.0078
Survival Probability (%)
Time since randomisation (months)
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)
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)

C



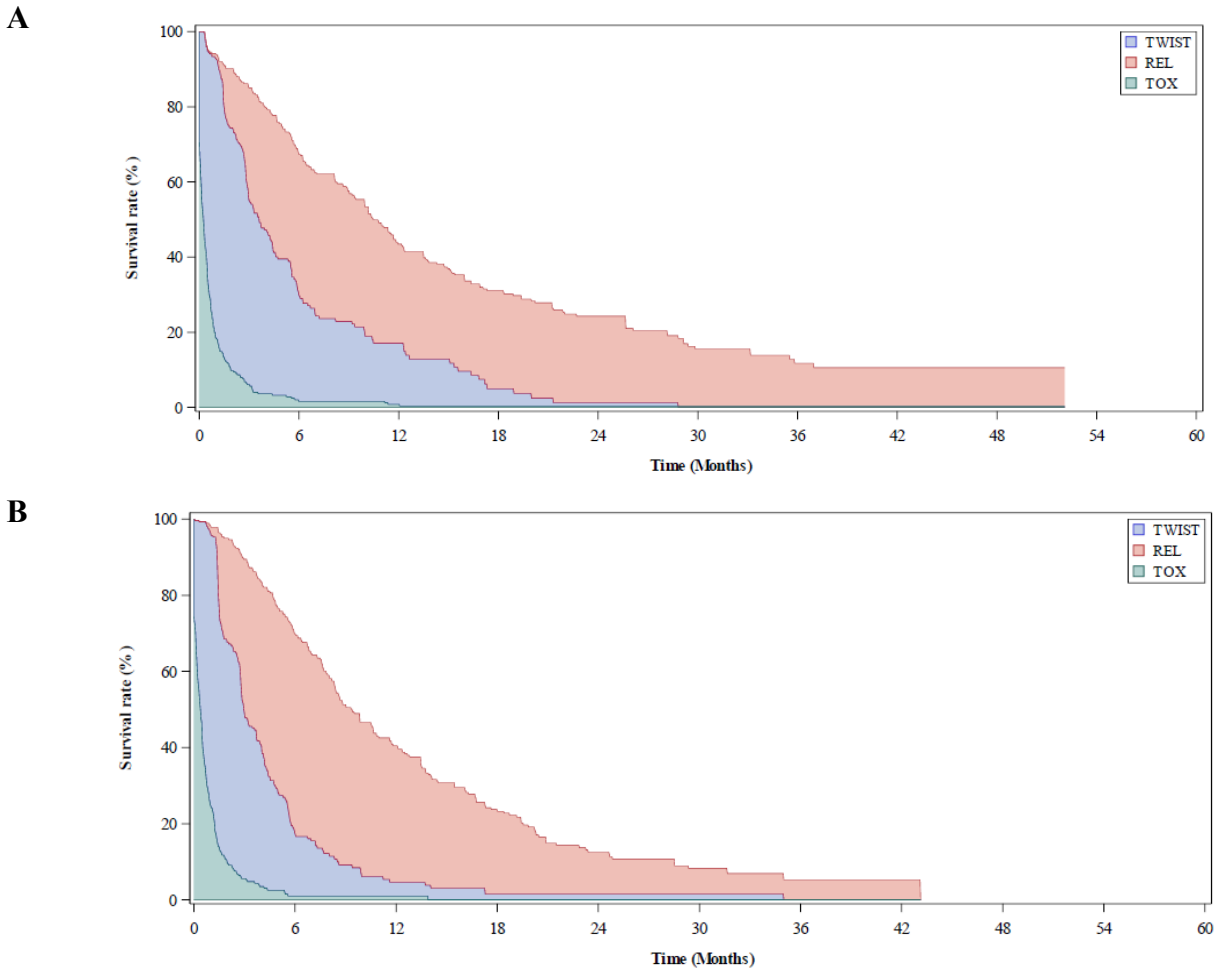
Supplementary Figure 2. Kaplan-Meier plots of exploratory long-term overall survival in the intent-to-treat population (A), non-squamous population (B), and second-line population (C)

Abbreviations: CI = confidence interval; D = docetaxel and placebo; DP = docetaxel and plinabulin; HR = hazard ratio; n = number of patients.



Supplementary Figure 3. Progression-free survival in key patient subgroups

Abbreviations: CI = confidence interval; D = docetaxel and placebo; DP = docetaxel and plinabulin; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand 1; RoW = rest of the world.



Supplementary Figure 4. Q-TWiST quality of life after treatment with plinabulin plus docetaxel (A) and docetaxel plus placebo (B)

Abbreviations: REL = time after event; TOX = time before an event; Q-TWiST = Quality-adjusted Time Without Symptoms of Disease and Toxicity; TWiST = Time Without Symptoms of Disease and Toxicity.