PP01.45: Phase 3 Study of Plinabulin/Docetaxel vs. Docetaxel in 2L/3L EGFR Wild Type NSCLC (DUBLIN-3): Post PD-1 Progression and Brain Metastasis Analyses

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INTRODUCTION

Background: The phase 3 DUBLIN-3 (NCT02504489) trial enrolled patients from 2015 through 2021, has demonstrated a statistically significant improvement in overall survival (OS) with "plinabulin + docetaxel" vs SOC docetaxel in 2L/3L advanced and metastatic non-small cell lung cancer (NSCLC) with EGFR wild type (Lancet Resp Med 12:775, 2024). During the DUBLIN-3 enrollment period, the treatment landscape for NSCLC was rapidly changing and limited number of patients received a prior checkpoint inhibitor. Additionally, NSCLC patients with intracranial progression are associated with poor prognosis.

Plinabulin is a brain-penetrating, unique tubulin binder with dendritic cell maturation mechanism, which can pass blood brain barrier with benefit in glioblastoma animal model, so we performed a post-hoc analysis on patients who developed intracranial progression along with evaluating the survival of non-squamous patients who had rapid progression on prior PD-1/L1 inhibitors with PFS >=3 months.

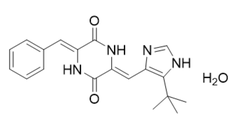
DISCUSSION AND CONCLUSION

There is an unmet medical need for new treatment options in NSCLC after progression with platinum-based chemotherapy and immunotherapy, with nine phase 3 study, including ADC and PD-1/L1 inhibitor combination failing to show OS benefit vs. SOC docetaxel. Plinabulin displays unique immune-oncology effects by inducing dendritic cell maturation and T-cell activation, which could mitigate "acquired resistance" to ICI.

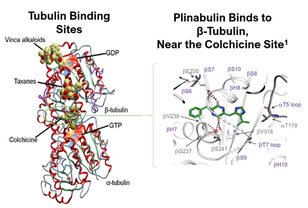
In our post-hoc analysis, plinabulin/docetaxel combination produced clinically meaningful anti-cancer benefit in **OS, PFS, and ORR** for this hard-to-treat population, with additional **benefit in metastasis-free survival** and **reduced brain metastasis**.

We plan to open soon the "A Global, Multicenter, Randomized, Double-blinded, Phase 3 Study of Docetaxel + Plinabulin vs. Docetaxel + Placebo in Patients with Advanced or Metastatic Non-squamous Non-Small Cell Lung Cancer with EGFR Wild Type After Progressing on Prior Immunotherapy (Anti-PD-1/L1) and Platinum-based Chemotherapy Concurrently or Sequentially (DUBLIN-4)"

METHODS



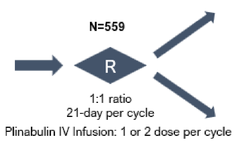
Active Ingredient
Plinabulin monohydrate



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

Study Plan	Primary endpoint	Secondary endpoints
• Global, randomized, single-blinded (patients only) – 58 clinical sites (ICON CRO) • Stratified by region (Asia/non-Asia), prior line (2L or 3L), ECOG (0-1/2), Prior PD-1/PD-L1 (yes/no)	**Overall survival (OS)**	• 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]**



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)

RESULTS

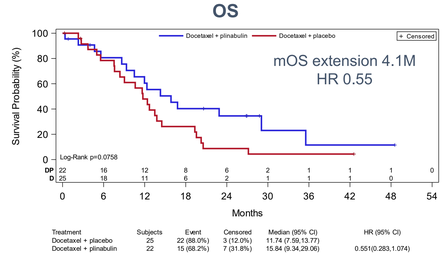
Between 30-Nov-2015 and 06-Jan-2021, 559 patients received either docetaxel plus plinabulin (DP, n=278) or docetaxel plus placebo (D, n=281). Median OS was 10·5 months (95% CI 9·34-11·87) in the plinabulin group compared with 9·4 months (8·38-10·68) in the control group (stratified HR 0·82, 95% CI 0·68-0·99; p=0·0399), and significant reduction in grade 4 neutropenia in day 8 all cycles (DP: 5.13% vs. D: 33.58%, p<0.0001).

- At 24-months follow-up after database lock, post-hoc analysis showed that **non-squamous patients** had better survival: **median OS was 11.4 months (95% CI: 9.37, 12.95) in the DP Arm (n=154) vs. 8.8 months (95% CI:7.73, 10.65) in the D Arm (n=178; stratified HR 0.72 [95% CI 0.57, 0.92]; p=0.0078).**
- For the **non-squamous patients who progressed on prior PD-1/L1 inhibitors (PFS >=3 months)** in DP (n=22) and D (n=25) arms, DP arm showed clinically meaningful improvement in **OS (15.8 vs. 11.7 months, HR=0.55, p=0.076), progression-free survival (PFS) (5.6 vs. 3.8 months, HR=0.67, p=0.23), and objective response rate (ORR) (18.2% vs. 8.0%, p=0.30).**
- In the ITT population,
  - The exposure-adjusted grade 3/4 AE events and grade 4 AE events were significantly less in DP vs D arm. Grade 3/4 Events: 9.76 vs. 10.93 event rate per year, p=0.0235; grade 4 Events: 1.69 vs.3.08 event rate per year, p<0.0001.
  - DP improved **metastasis-free survival** (the length of time from the start of treatment for cancer that a subject is still alive and the cancer has not spread to other parts of the body) at **15.34 months vs. 7.7 months in the D arm (HR = 0.516; p=0.0012)**, equating to a 7.6-month improvement.
  - Based on the brain MRI data, **brain metastasis was reduced in DP (12/278; 4.32%) vs. D (22/281; 7.83%) arm (p=0.0826).**

Plinabulin Mechanism Enriched Population
(Post-hoc Analysis)

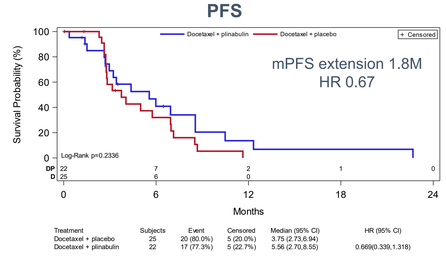
Non-squamous NSCLC, prior PD-1/L1 PFS >=3 months - Improved OS, PFS, and ORR in DP vs. D

OS



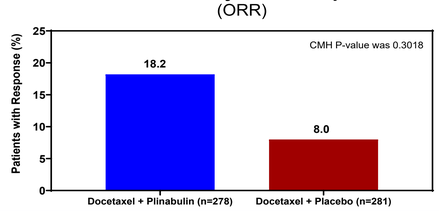
Treatment	Subjects	Event	Censored	Median (95% CI)	HR (95% CI)
Docetaxel + placebo	25	22 (88.0%)	3 (12.0%)	11.74 (7.59,13.77)	
Docetaxel + plinabulin	22	15 (68.2%)	7 (31.8%)	15.84 (9.34,29.06)	0.551(0.283,1.074)

PFS



Treatment	Subjects	Event	Censored	Median (95% CI)	HR (95% CI)
Docetaxel + placebo	25	20 (80.0%)	5 (20.0%)	3.75 (2.73,6.94)	
Docetaxel + plinabulin	22	17 (77.3%)	5 (22.7%)	5.56 (2.70,8.55)	0.669(0.339,1.318)

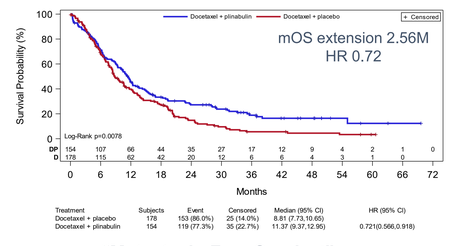
Confirmed Objective Response
(ORR)



ITT Population
(Post-hoc Analysis)

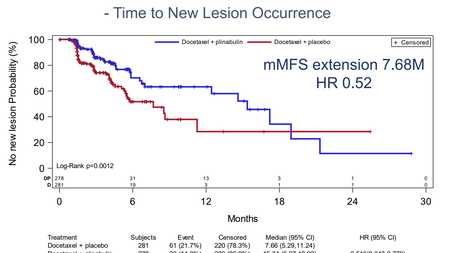
Non-squamous NSCLC - 24M after database lock in DP vs. D

OS



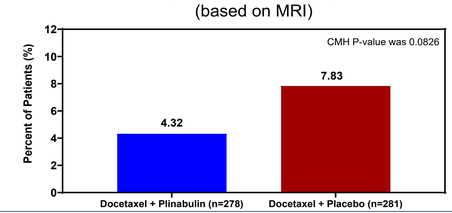
Treatment	Subjects	Event	Censored	Median (95% CI)	HR (95% CI)
Docetaxel + placebo	178	153 (86.0%)	25 (14.0%)	8.81 (7.73,10.65)	
Docetaxel + plinabulin	154	119 (77.3%)	35 (22.7%)	11.37 (9.37,12.95)	0.721(0.566,0.918)

"Metastasis-Free Survival"
- Time to New Lesion Occurrence



Treatment	Subjects	Event	Censored	Median (95% CI)	HR (95% CI)
Docetaxel + placebo	281	61 (21.7%)	220 (78.3%)	7.66 (5.29,11.24)	
Docetaxel + plinabulin	278	39 (14.0%)	239 (86.0%)	15.34 (6.97,18.92)	0.516(0.343,0.776)

New Metastasis in Brain
(based on MRI)



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