Plinabulin/Docetaxel vs. Docetaxel in Survival Benefits of 2L/3L EGFR Wild-Type NSCLC after Platinum Regimens (DUBLIN-3): a Randomized Phase 3 Trial

Trevor Feinstein, MD[1], Baohui Han, MD[2], Yuankai Shi, MD[3], Gongyan Chen, MD[4], Yu Yao, PhD[5], Chunhong Hu, MD[6], Jianhua Shi[7], Jifeng Feng, PhD[8], Huijuan Wu[9], Ying Cheng, MD[10], Qi-sen Guo[11], Zhijun Jie, MD[12], Feng Ye[13], Yiping Zhang, MD[14], Zhihua Liu, MD[15], Weidong Mao, MS[16], Lyudmila Bazhenova[17], Yanping Wu, MS[18], Lan Huang, PhD[18] and Yan Sun, MD[3].

[1]Piedmont Cancer Institute, GA, USA; [2]Shanghai Chest Hospital, Shanghai, CHN; [3]National Cancer Center, Beijing, CHN; [4]Harbin Medical University Cancer Hospital, Heilongjiang Province, CHN; [5]The First Affiliated Hospital of Xi'an Jiaotong University, Shanxi Province, CHN; [6]The Second Xiangya Hospital of Central South University, Hunan Province, CHN; [7]Linyi Cancer Hospital, Shandong Province, CHN; [8]Jiangsu Cancer Hospital, Jiangsu Province, CHN; [9]Henan Cancer Hospital, Henan Province, CHN; [10]Jilin Cancer Hospital, Jilin Province, CHN; [11]Shandong Cancer Hospital, Shandong Province, CHN; [12]Shanghai Fifth People's Hospital, Shanghai, CHN; [13]The First Affiliated Hospital of Xiamen University, Fujian Province, CHN; [14]Zhejiang Cancer Hospital, Zhejiang Province, CHN; [15]Jiangxi Cancer Hospital, Jiangxi Province, CHN; [16]Jiangyin People's Hospital, Jiangsu Province, CHN; [17]University of California San Diego, CA, USA; [18]BeyondSpring Pharmaceuticals Inc, NY, USA

FPN: 1358P
Clinical trial registration: NCT02504489

Introduction

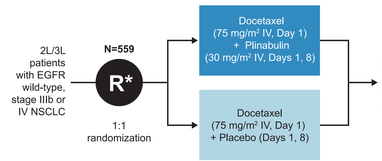
- Docetaxel-based therapies are the standard of care for patients with second/third line (2L/3L) epidermal growth factor receptor (EGFR) wild-type non-small cell lung cancer (NSCLC).
- In first line (1L) patients with EGFR wild-type NSCLC, response rates to platinum-based chemotherapy vary from 20–40%,[1] with increases to 55–67% following the addition of programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors.[2,3]
- As many patients (>60%) experience progressive disease, there remains an unmet need for effective and tolerable treatments for 2L/3L advanced or metastatic NSCLC.[4]
- Recent Phase 3 studies assessing PD-1/L1 inhibitors combined with tyrosine kinase inhibitor or anti-TIGIT, and novel antibody-drug conjugate agents, failed to show an overall survival (OS) benefit in this population vs. docetaxel.
- Plinabulin is a first-in-class agent that activates the adaptive and innate immune system via inducing dendritic cell (DC) maturation, with the potential to overcome immunotherapy resistance.[5–7]

Methods

Study Design

- DUBLIN-3 (NCT02504489) was a single blind, randomized, Phase 3 trial in 58 centers in the United States (US), China and Australia (**Figure 1**).

Figure 1. DUBLIN-3 study design



* Patients were randomized in a 1:1 ratio; randomization was stratified by region (Asia/non-Asia), prior line (2L or 3L), Eastern Co-operative Oncology Group (ECOG, 0–1/2), prior PD-1/PD-L1 (yes/no).
2L/3L, second/third line; EGFR, epidermal growth factor receptor; IV, intravenous; N, total number of patients randomized; NSCLC, non-small cell lung cancer; R, randomization.

Patients	Study endpoints
Key patient inclusion criteria:	OS
Non-squamous or squamous NSCLC	PFS
Stage IIIb/IV	ORR
ECOG ≤2	DoR
Disease progression during or after treatment with one or two platinum-containing regimens	Proportion of patients without severe neutropenia
≥1 measurable lung lesion	Incidence of TEAEs and SAEs
Prior checkpoint inhibitor therapy was permitted	Grade 4 neutropenia
	Q-TWiST

DoR, duration of response; ECOG, Eastern Co-Operative Oncology Group; NSCLC, non-small cell lung cancer; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; Q-TWiST, Quality-adjusted time without symptoms of disease progression or toxicity; Quality-adjusted time without symptoms of disease progression or toxicity; SAE, serious adverse events; TEAE, treatment-emergent adverse events.

Results

Patient baseline demographics and characteristics

- Between 30th of November 2015 and 6th of January 2021, 559 patients were enrolled and randomized to either docetaxel + plinabulin (n=278) or docetaxel + placebo (n=281) (**Table 1**).

Table 1. Baseline demographics and 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	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)
Cancer Stage, n (%)		
IIIB	41 (14.6)	50 (18.0)
IV	236 (84.0)	224 (80.6)
Received prior PD-1/PD-L1 therapy, n (%)	57 (20.3)	49 (17.6)
Lines of prior therapy, n (%)		
First-line	212 (75.4)	204 (73.4)
Second-line	69 (24.6)	74 (26.6)
Previous radiotherapy, n (%)	84 (29.9)	87 (31.3)
Previous surgery, n (%)	138 (49.1)	123 (44.2)

ECOG, Eastern Co-operative Oncology Group; n, number of patients, N, total number of patients; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

Efficacy summary

- In the final intention to treat (ITT) analysis plinabulin significantly improved OS, PFS and ORR (**Table 2**).

Table 2. Efficacy summary

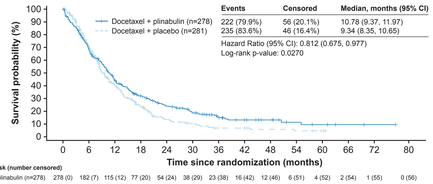
ITT Population	Docetaxel + plinabulin (N=278)	Docetaxel + placebo (N=281)	p-value	HR (95% CI)
OS (median)	10.5 M	9.4 M	0.0399	0.82 (0.68, 0.99)
OS (mean)	15.1 M	12.8 M	0.0332	
PFS* (median)	3.3 M	2.8 M	0.0174	0.79 (0.66, 0.96)
PFS* (mean)	4.9 M	4.0 M	0.0250	
ORR* (%)	14.0	8.5	0.0404	
DoR (median)	8.3	6.1	0.0606	0.56 (0.30, 1.03)

*Central lab radiography review.
CI, confidence interval; DoR, duration of response; HR, hazard ratio; ITT, intention to treat; M, months; N, total number of patients; OS, overall survival; ORR, overall response rate; PFS, progression-free survival.

OS benefit after long-term OS follow-up

- A sustained OS benefit was demonstrated in the ITT population after long-term follow-up for further 24-months beyond final database lock:
  - Median OS 10.8 months in the docetaxel + plinabulin vs. 9.3 months in the docetaxel + placebo (hazard ratio [HR] 0.81, p=0.027; **Figure 2**).
  - In patients with non-squamous NSCLC, median OS 11.4 months in docetaxel + plinabulin (n=154) vs. 8.8 months in docetaxel + placebo (n=178) (HR 0.72, p=0.0078).

Figure 2. Long-term OS (ITT population)



HRs and two-sided 95% CIs were estimated with a Cox proportional hazards model with treatment as the only covariate.
CI, confidence interval; HR, hazard ratio; ITT, intention to treat; n, total number of patients; OS, overall survival.

Safety

- Similar percentages of patients experienced ≥1 TEAE; 99.6% and 99.3% in the docetaxel + plinabulin and docetaxel + placebo arms, respectively (**Table 3**).

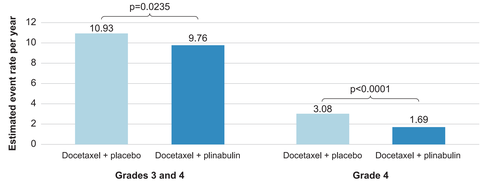
Table 3. Overall summary of TEAEs (safety population)

	Docetaxel + placebo (N=278)	Docetaxel + plinabulin (N=274)
Any TEAE, n (%)	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 docetaxel modification	108 (38.8)	135 (49.3)
Leading to plinabulin modification	N/A	164 (59.9)
Leading to permanent discontinuation of docetaxel	30 (10.8)	34 (12.4)
Leading to permanent discontinuation of plinabulin	N/A	34 (12.4)

Safety data was analyzed using descriptive statistics.
n, number of patients; N, total number of patients; N/A, not applicable; TEAE, treatment-emergent adverse event.

Reduced exposure-adjusted AE rates

Figure 3. Summary of Grade 3 or 4 exposure-adjusted AE rates (safety population)



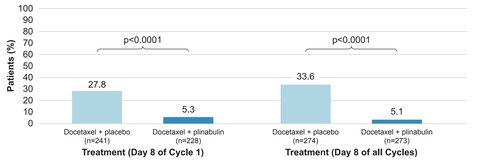
AE, adverse event.

- In the docetaxel + plinabulin arm, 16 (6.0%) patients used docetaxel for ≥12 cycles vs. 9 (3.0%) patients in the docetaxel + placebo arm.

Reduced neutropenia and G-CSF use

- The incidence of any grade neutropenia was lower in the docetaxel + plinabulin arm vs. the docetaxel + placebo arm (142 [51.8%] vs. 196 [70.5%] patients).
- Incidence of Grade 4 neutropenia was significantly lower in the docetaxel + plinabulin vs. docetaxel + placebo arm on Day 8 Cycle 1 (difference -22.54%; 95% confidence interval [CI]: -28.89, -16.18; p<0.0001) and Day 8 in all cycles (difference -28.45; 95% CI: -34.62, -22.27; p<0.0001) (**Figure 4**).
- Hospital admission due to febrile neutropenia was lower in the docetaxel + plinabulin arm (7 [2.6%] vs. 14 [5.0%] patients).

Figure 4. Patients with ANC <0.5 x 10^9/L on Day 8 of Cycle 1 and Day 8 in all cycles (ITT population)



ANC, absolute neutrophil count; ITT, intention to treat; n, number of patients.

- Post-hoc analysis showed reduced granulocyte-colony stimulating factor (G-CSF) use in the docetaxel + plinabulin arm (152 [56%] patients) compared with the docetaxel + placebo arm (182 [66%] patients) and at cycles 1 to 4 (**Table 4**).

Table 4. G-CSF use in each treatment cycle

Treatment cycle	Docetaxel + plinabulin	Docetaxel + placebo
Any cycle, n/N (%)	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)

G-CSF, granulocyte-colony stimulating factor; n, number of patients; N, total number of patients.

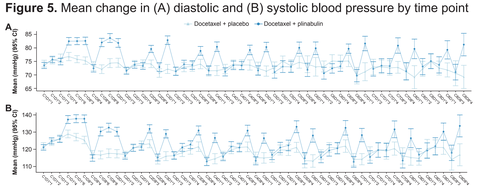
Transient hypertension/increase blood pressure

- A higher percentage of patients had increased blood pressure in the docetaxel + plinabulin arm compared with the docetaxel + placebo arm (33.9% vs. 5.8%).
- Grade 3 events occurred more frequently in the docetaxel + plinabulin arm vs. the docetaxel + placebo arm (50 [18.2%] vs. 8 [2.9%] patients); there were no events of Grade ≥4.
- Both diastolic and systolic blood pressure increased following plinabulin infusions and returned to baseline on Day 1 and Day 8 of each cycle (**Figure 5**).
- The observed hypertension was transient and most incidences resolved within 4–6 hours.
- Only 34 (12.4%) patients in the docetaxel + plinabulin arm and 4 (1.4%) patients in the docetaxel + placebo arm had hypertension or increased blood pressure that required medication intervention.
- Only 2 (0.7%) patients (both in the docetaxel + plinabulin arm) required dose reduction due to increased blood pressure.

Gastrointestinal (GI) TEAEs

- Patients in the docetaxel + plinabulin arm reported more Grade 3 or 4 GI TEAEs compared to patients in the docetaxel + placebo arm (16.8% vs. 2.9%), with higher rates of Grade 3 or 4 diarrhea (8.8% vs. 1.1%) and vomiting (2.2% vs. 0.4%).

Figure 5. Mean change in (A) diastolic and (B) systolic blood pressure by time point



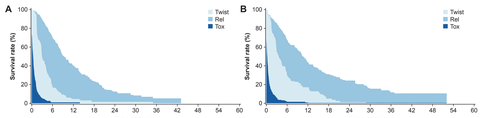
*1: pre-dose docetaxel; *2: end of infusion docetaxel; *3: pre-dose plinabulin; *4: end of infusion plinabulin; *6: 30 minutes post dose plinabulin; *8: 60 minutes post dose plinabulin.
C, cycle; CI, confidence interval; D, study day.

- The trial protocol was amended to increase infusion time from 30 to 60 minutes and allowed prophylactic anti-diarrhea medication, which reduced Grade 3 and 4 GI TEAEs; bowel obstruction (8.1% to 4.3%), diarrhea (14.0% to 5.5%), and nausea (2.3% to 0.6%).
- Nearly all patients with bowel obstruction/ileus recovered and these patients had similar OS to the rest of the population.

Improved quality of life (QoL)

- Exploratory analysis showed better QoL based on Q-TWiST in the docetaxel + plinabulin arm (**Figure 6**), with a clinically meaningful gain to control of 18.5% (p=0.0393).

Figure 6. Docetaxel + placebo (A) Q-TWiST QoL after treatment with docetaxel + plinabulin (B)



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; QoL, quality of life.

Conclusions

- Plinabulin is a first-in-class small molecule agent with potent real-time dendritic cell maturation activity for a durable anti-cancer benefit.
  - The addition of plinabulin to standard of care docetaxel therapy significantly improved OS, PFS, ORR and 2- and 3- year OS rates.
  - Additional 24-month follow-up data indicated sustained survival benefit.
- Docetaxel + plinabulin combination is well tolerated, with decreased severe neutropenia and improved QoL compared with docetaxel + placebo.
  - Plinabulin significantly decreased the incidence of Grade 4 neutropenia.
  - Increased blood pressure following plinabulin infusion was transient and most patients did not require anti-hypertensive medication.
  - GI events were manageable with dose adjustments or supportive care.
- **Docetaxel + plinabulin combination has a favorable benefit/risk ratio and could be considered a new therapy option for 2L/3L treatment in patients with advanced or metastatic EGFR wild-type NSCLC.**

Contact
Trevor Feinstein
tfeinstein@piedmontcancerinstitute.com

Disclosures
Trevor Feinstein, MD has received research funding from BeyondSpring Pharmaceuticals, Inc. to conduct this trial and is a speaker for Sanofi and Sobi.

Funding Source
This study was funded by BeyondSpring Pharmaceuticals, Inc.

References
1. Sirohi B, et al. *J Thorac Oncol* 2007;2(8):735–40;
2. Park SE, et al. *J Thoracic Oncol* 2018;13(1):106–11;
3. Langer CJ, et al. *Lancet Oncol* 2016;17(11):1497–508;
4. Alex F and Alfredo A. *Expert Rev Anticancer Ther.* 2020;20(11):931-937;
5. Natoli M, et al. *Front Oncol* 2021;11:644608;
6. Tonra JR, et al. *Cancer Chemother Pharmacol* 2020;85:461–68;
7. Neri S. *Cancer Res* 2020;80(suppl):4449.

Acknowledgments
- We would like to thank all the patients and their families for their participation and essential role in the study.
- We would also like to thank all the investigators and medical staff from 58 sites in the US, China and Australia and the study team for their contribution in the study.
- A special thank you to: Drs. Baohui Han, Yuankai Shi, Gongyan Chen, Yu Yao, Chunhong Hu, Jianhua Shi, Jifeng Feng, Huijuan Wu, Ying Cheng, Qi-sen Guo, Zhijun Jie, Feng Ye, Yiping Zhang, Zhihua Liu, Weidong Mao, Liangming Zhang, Junguo Lu, Jun Zhao, Lyudmila Bazhenova, Jimmy Ruiz, Goetz H Kloecker, Kalmadi R Sujith, Ira A Oliff, Matthew Wong, Bin Liu, Yanping Wu, Lan Huang, Yan Sun, and the Dublin-3 study group; Feng Luo, Jian-ying Zhou, Hongming Pan, Huaqing Wang, Chunling Liu, Lejie Cao, Chao Hui Huang, Eddie Thara, Xiaoling Li, Da Jiang, Rex B Mowat, John S Hrom, Adnan Nagrial, Vikram Jain, Nagla A Karim, Leonid V Shunyakov, Andrew Kiberu, Ross Jennens, Ken Lloyd, Zhongkun Wang, Lihua Du, Helen Li.
- Finally, we would like to thank Alchemy Medical Writing Ltd for medical writing and editorial assistance, TCM Groups, Inc. for statistical analysis support and BeyondSpring Pharmaceuticals, Inc. for manuscript and congress material support.

Use the QR code to find more information about the DUBLIN-3 Randomized Phase 3 Trial