2. Synopsis

Title of Study: A Randomized, Open-Label Phase 2 Study of EC145 Single-agent and the Combination of EC145 plus Docetaxel Versus Docetaxel Alone in Participants With Folate-Receptor Positive [FR(++)] Second Line NSCLC

Number of Investigator(s): This multicenter study included 52 principal investigator(s).

Study Center(s): This study was conducted at 52 study center(s) in 10 countries.

Publications Based on the Study:

Hanna N, Juhász, E, Cainap C, et al. TARGET: A randomized, phase II trial comparing vintafolide versus vintafolide plus docetaxel, versus docetaxel alone in second-line treatment of folate-receptor-positive nonsmall cell lung cancer (NSCLC) patients. Ann Oncol 25 (suppl 4; abstr LBA40_PR); 2014.

Edelman MJ, Ma H, Perez W, Adjei AA, Hanna N. A randomized, open-label phase II study of single-agent vintafolide versus vintafolide plus docetaxel versus docetaxel alone in second-line NSCLC patients with all target lesions expressing folate-receptor (TARGET). J Clin Oncol 31 (suppl; abstr TPS8125); 2013.

Length of Study:
Date of first patient enrolled: 31 May 2012
Data cutoff date: 14 February 2014

Phase of Development: 2

Objectives:

Primary

- Progression-free survival (PFS)

Secondary

- Overall tumor response rate (ORR=complete response [CR]+partial response [PR]), Duration of tumor response (DOR), Disease control rate (DCR=CR+PR+stable disease [SD]), Duration of disease control
- Overall survival (OS)

Safety

- Evaluate the safety and tolerability of vintafolide single-agent and in combination with docetaxel in this patient population
- Evaluate the safety and tolerability of etarfolatide [EC20] labeled with technetium-99m (^{99m}Tc-etarfolatide)

Study Design: This was an international, multicenter, centrally-randomized, open-label, Phase 2, 3-arm study comparing single-agent vintafolide, vintafolide+docetaxel combination treatment, and single-agent docetaxel given until disease progression or unacceptable toxicity in patients with nonsmall cell lung cancer (NSCLC) who had failed 1 prior chemotherapy and who had all RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1-defined target lesions expressing the folate receptor.

Number of Patients:

	Single-agent vintafolide arm	Vintafolide+docetaxel combination arm	Single-agent docetaxel arm
Planned	60	60	60
Randomized	67	68	68
Treated	63	68	68
Analyzed	63	68	68

Diagnosis and Main Criteria for Inclusion: Patients, ≥18 years old, with a histology-confirmed diagnosis of NSCLC (adenocarcinoma, squamous, adenosquamous carcinoma, or adenocarcinoma with other NSCLC variants of the lung), Stage IIIB or IV, with all RECIST version 1.1-defined target lesions positive for the folate receptor [FR(100%)] by SPECT scan, and only 1 prior systemic therapy for advanced disease.

Study Drug, Dose, and Mode of Administration:

Vintafolide was administered as a 2.5 mg IV bolus injection on Days 1, 4, 8, and 11 during Weeks 1 and 2 of a 3-week cycle.

^{99m}Tc-etarfolatide, Dose, and Mode of Administration:
Prior to SPECT imaging, patients received 1 IV injection of 0.5 mg folic acid, 1 to 3 minutes before a 1 to 2 mL IV injection of 0.1 mg etarfolatide labeled with 20 mCi to 25 mCi of ^{99m}Tc.

Reference Treatment, Dose, and Mode of Administration:
Docetaxel was administered at 75 mg/m^2 IV over 1 hour on Day 1 of a 3-week cycle; must have been in conjunction with Day 1 of vintafolide administration for patients in the combination treatment arm.

Duration of Treatment:
Patients were to continue treatment until disease progression or unacceptable toxicity.
Patients in the combination treatment arm who discontinued docetaxel due to unacceptable docetaxel toxicity could have continued on single-agent vintafolide.

Criteria for Evaluation:
Efficacy: PFS, ORR, DOR, DCR, Duration of disease control, OS
Safety: Adverse events (AEs), Serious AEs (SAEs), Deaths

Statistical Evaluation Methods:
The following data analysis sets were defined:

- Efficacy analysis population: The efficacy analysis population consisted of all randomized patients who received 1 or more doses of vintafolide and/or docetaxel, by planned treatment.
- Safety analysis population: The safety analysis population consisted of all randomized patients who received at least 1 dose of vintafolide and/or docetaxel, by actual treatment
- ^{99m}Tc-etarfolatide safety analysis population: The safety analysis population for ^{99m}Tc-etarfolatide safety reporting consisted of all patients who received ^{99m}Tc-etarfolatide.

Efficacy: The primary efficacy endpoint for this study was PFS, defined as the duration from randomization to the first occurrence of either PD or death. The primary analysis was censored for post discontinuation anticancer therapy and missed scheduled assessments. The primary objective of this study was to compare PFS in the combination treatment arm (vintafolide+docetaxel) versus single-agent docetaxel and in the single-agent vintafolide treatment arm versus single-agent docetaxel. The primary comparisons were made using the unstratified log-rank test. For each comparison, 94 PFS events from 120 patients would have provided approximately 75% power to detect a hazard ratio (HR) equal to 0.67. Assuming the median PFS for docetaxel is 3 months, these HRs corresponded to 4.5 months in the experimental treatment arms (i.e., a 50% improvement in the median PFS). The significance level for each PFS analysis was 1-sided alpha = 0.10 with no adjustments for multiple testing.
An interim PFS analysis for futility was planned and reviewed by an independent Data Safety Monitoring Board (DSMB) for each of the comparisons of interest (i.e., vintafolide+docetaxel vs single-agent docetaxel, single-agent vintafolide vs single-agent docetaxel). The interim analysis occurred when approximately 50% of the PFS events (approximately 47) occurred for each comparison.
Long-term follow-up is to be conducted on all randomized and treated patients. It is expected that this follow-up will continue until the censoring rate for OS is ≤30% for final analysis of OS. In the final statistical analysis plan (SAP), the period of long-term follow-up was defined to have at least 6 months follow-up for the last patient in the study. Final OS analysis is to occur when at least 144 events of death have occurred across all 3 treatment arms.
Safety: The assessment of safety was based on extent of exposure, AEs, and laboratory test results.

Summary:
Results presented in this clinical study report are based on the analysis of data collected up to and including 14 February 2014 for the primary PFS analysis. The PFS results are mature with a total of 165 PFS events and 17.1% of patients censored for a PFS event. The OS results are still immature with a total of 92 deaths and 53.8% of patients censored for the OS analysis. The final OS analysis will be performed when at least 70% of the treated patients have had an OS event.
This study was designed as a 3-arm study with 2 separate efficacy comparisons, both against single-agent docetaxel. Each comparison was reviewed in the interim efficacy analysis and the DSMB unanimously recommended that the

vintafolide+docetaxel combination and the single-agent docetaxel treatment arms continue as planned. They also unanimously recommended that the single-agent vintafolide treatment arm be closed for enrollment since it was not likely to be superior to the single-agent docetaxel treatment arm based on the interim analysis results of the primary efficacy endpoint, PFS. Since there was no evidence of harm, they recommended that patients in the single-agent vintafolide treatment arm be offered continued treatment with vintafolide and that all patients in that treatment arm be followed for survival.

Study Patients

Of the 203 randomized patients, 199 patients received at least 1 dose of vintafolide and/or docetaxel and were included in the efficacy analysis population. Overall, demographic and baseline disease characteristics were similar between the treatment arms (Table 1). Study patients ranged in age from 35 to 82 years of age. The majority of patients overall were male (72.4%), White (94.5%), and middle-aged (median age: 64 years) with a good ECOG performance status (ECOG 0-1 in 99.5% of patients). Most patients were current (29.1%) or former smokers (54.8%). Overall, the majority of patients in the efficacy analysis population had Stage IV disease (84.4%; Table 2) and a pathologic diagnosis of adenocarcinoma (59.8%). Of the 199 randomized and treated patients, 169 had been treated with 1 line of cytotoxic therapy and 30 patients had been treated with an EGFR inhibitor either alone (n=7) or in combination with cytotoxic therapy (n=23).

Table 1 Patient and Disease Characteristics – Efficacy Analysis Population

	Single-agent Vintafolide N=63	Vintafolide+ Docetaxel N=68	Single-agent Docetaxel N=68	All N=199
Gender (n)	**63**	**68**	**68**	**199**
Male, n (%)	45 (71.4%)	47 (69.1%)	52 (76.5%)	144 (72.4%)
Female, n (%)	18 (28.6%)	21 (30.9%)	16 (23.5%)	55 (27.6%)
Age (n)	**63**	**68**	**68**	**199**
Mean ±SD (years)	63.8±8.51	62.9±8.09	63.0±7.33	63.2±7.95
Median (years)	64.0	63.5	63.0	64.0
Range (years)	45-80	35-82	43-77	35-82
Race (n)	**63**	**68**	**68**	**199**
Asian, n (%)	-	1 (1.5%)	2 (2.9%)	3 (1.5%)
Black/African American, n (%)	-	1 (1.5%)	1 (1.5%)	2 (1.0%)
White, n (%)	60 (95.2%)	65 (95.6%)	63 (92.6%)	188 (94.5%)
Missing, n (%)	3 (4.8%)	1 (1.5%)	2 (2.9%)	6 (3.0%)
Ethnicity (n)	**63**	**68**	**68**	**199**
Hispanic or Latino, n (%)	1 (1.6%)	-	-	1 (0.5%)
Not Hispanic or Latino, n (%)	59 (93.7%)	67 (98.5%)	66 (97.1%)	192 (96.5%)
Missing, n (%)	3 (4.8%)	1 (1.5%)	2 (2.9%)	6 (3.0%)
ECOG performance status (n)	**63**	**68**	**68**	**199**
0, n (%)	14 (22.2%)	18 (26.5%)	18 (26.5%)	50 (25.1%)
1, n (%)	48 (76.2%)	50 (73.5%)	50 (73.5%)	148 (74.4%)
2, n (%)	1 (1.6%)	-	-	1 (0.5%)
Smoking status (n)	**63**	**68**	**68**	**199**
Never smoked, n (%)	15 (23.8%)	7 (10.3%)	10 (14.7%)	32 (16.1%)
Formerly smoked, n (%)	29 (46.0%)	43 (63.2%)	37 (54.4%)	109 (54.8%)
Currently smoke, n (%)	19 (30.2%)	18 (26.5%)	21 (30.9%)	58 (29.1%)
Type of cancer (n)	**63**	**68**	**68**	**199**
Adenocarcinoma, n (%)	37 (58.7%)	39 (57.4%)	43 (63.2%)	119 (59.8%)
Adenosquamous carcinoma, n (%)	2 (3.2%)	2 (2.9%)	5 (7.4%)	9 (4.5%)
Adenocarcinoma with other NSCLC variants, n (%)	2 (3.2%)	2 (2.9%)	1 (1.5%)	5 (2.5%)
Squamous cell carcinoma, n (%)	22 (34.9%)	25 (36.8%)	19 (27.9%)	66 (33.2%)

Table 2 Randomization Data by Stratification Factor – All Randomized Patients

	Single-agent Vintafolide N=67	Vintafolide+ Docetaxel N=68	Single-agent Docetaxel N=68	All N=203
Time since last chemotherapy (n)	**67**	**68**	**68**	**203**
<3 months, n (%)	34 (50.7%)	33 (48.5%)	34 (50.0%)	101 (49.8%)
≥3 months, n (%)	33 (49.3%)	35 (51.5%)	34 (50.0%)	102 (50.2%)
Best response to last chemotherapy (n)	**67**	**68**	**68**	**203**
CR/PR/SD, n (%)	49 (73.1%)	49 (72.1%)	48 (70.6%)	146 (71.9%)
PD/Unknown, n (%)	18 (26.9%)	19 (27.9%)	20 (29.4%)	57 (28.1%)
Disease stage (n)	**67**	**68**	**68**	**203**
Stage IIIB, n (%)	12 (17.9%)	10 (14.7%)	9 (13.2%)	31 (15.3%)
Stage IV, n (%)	55 (82.1%)	58 (85.3%)	59 (86.8%)	172 (84.7%)
Prior treatment with EGFR inhibitor (n)	**67**	**68**	**68**	**203**
Yes, n (%)	11 (16.4%)	10 (14.7%)	9 (13.2%)	30 (14.8%)
No, n (%)	56 (83.6%)	58 (85.3%)	59 (86.8%)	173 (85.2%)

Efficacy

At the time of database lock on 14 February 2014, a total of 165 PFS events had occurred; 34 patients (17.1%) were censored for the PFS analysis. An overall summary of efficacy results is presented in Table 3.

Table 3 Primary and Secondary Efficacy Analyses Results

	Single-agent Vintafolide N=63	Vintafolide+ Docetaxel N=68	Single-agent Docetaxel N=68
Median PFS, months (95% CI)	1.6 (1.4, 3.2)	4.2 (2.8, 5.4)	3.3 (1.7, 4.2)
HR PFS (95% CI; unstratified analysis)	1.35 (0.92, 1.96)	0.75 (0.52, 1.09)	
One-sided p-value	0.0579[a]	0.0696	
Overall Response Rate	4 (6.3%)	15 (22.1%)	9 (13.2%)
Median Duration of Response, months (95% CI)	- (4.4, -)	4.2 (2.8, 4.7)	3.7 (0.8, -)
Disease Control Rate	26 (41.3%)	48 (70.6%)	41 (60.3%)
Median Duration of Disease Control, months (95% CI)	4.2 (3.2, 5.1)	5.4 (4.2, 6.1)	5.5 (4.1, 6.8)
Median OS, months (95% CI)	9.5 (5.6, -)	- (7.3, -)	8.8 (5.4, -)

[a] In favor of the single-agent docetaxel treatment arm.

Primary Efficacy Results

Efficacy results demonstrate that the pre-specified, primary endpoint of improved PFS over single-agent docetaxel was met by the vintafolide+docetaxel combination treatment arm. In patients with previously treated advanced NSCLC, the addition of vintafolide to docetaxel significantly improved median PFS compared to single-agent docetaxel (HR: 0.75, 95% CI: 0.52, 1.09; 1-sided p-value by un-stratified log-rank test: 0.0696; Table 3). In the unstratified analysis, median PFS was significantly longer in patients treated with single-agent docetaxel than in patients treated with single-agent vintafolide (HR: 1.35; 1-sided p-value by un-stratified log-rank test: 0.0579 in favor of the single-agent docetaxel treatment arm).

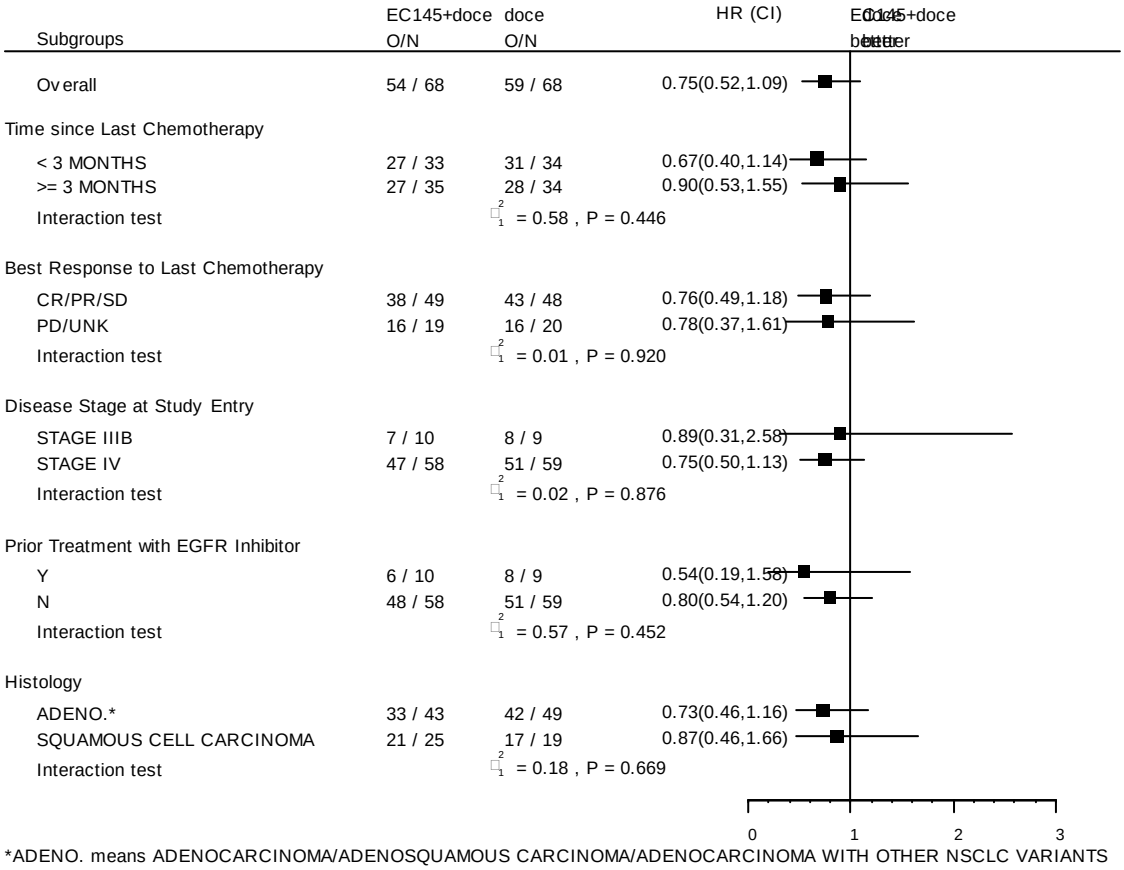
These primary efficacy analysis results were evaluated methodologically and were internally consistent and robust with no signs of systematic bias. All 4 sensitivity analyses were consistent with the primary PFS analysis in favor of vintafolide+docetaxel combination treatment over single-agent docetaxel treatment (Table 4).

Table 4 Sensitivity Analysis of PFS

	Sensitivity 1[a]		Sensitivity 2[b]		Sensitivity 3[c]		Sensitivity 4[d]	
	Vintafolide+ Docetaxel	**Single-agent Docetaxel**	**Vintafolide+ Docetaxel**	**Single-agent Docetaxel**	**Vintafolide+ Docetaxel**	**Single-agent Docetaxel**	**Vintafolide+ Docetaxel**	**Single-agent Docetaxel**
Number of PFS events, n (%)	55 (80.9%)	59 (86.8%)	64 (94.1%)	66 (97.1%)	55 (80.9%)	60 (88.2%)	46 (78.0%)	52 (85.2%)
Number censored, n (%)	13 (19.1%)	9 (13.2%)	4 (5.9%)	2 (2.9%)	13 (19.1%)	8 (11.8%)	13 (22.0%)	9 (14.8%)
Median PFS, months (95% CI)	4.2 (2.9, 5.4)	3.3 (1.7, 4.2)	3.5 (2.6, 4.3)	3.3 (1.7, 4.0)	4.2 (2.9, 5.4)	3.3 (1.7, 4.2)	4.1 (2.9, 5.4)	3.5 (2.6, 4.2)
HR (unstratified Cox model; 95% CI)	0.75 (0.52, 1.09)		0.80 (0.57, 1.14)		0.74 (0.51, 1.08)		0.80 (0.54, 1.19)	
One sided p-value (unstratified log-rank test)	0.0702		0.1115		0.0607		0.1376	

[a] Includes events regardless of intervening missed assessments.
[b] Considers discontinuation of study treatment or initiation of new anticancer therapy, whichever occurred later, to be a PD event for patients without documented PD/death.
[c] Considers all PFS events regardless of violations, discontinuation of study treatment, or change of treatment; missing assessments are excluded.
[d] Excludes patients who did not meet eligibility criteria and/or were granted eligibility waivers.

Consistent results across all subgroup analyses, defined by baseline patient and disease characteristics, were shown to favor vintafolide+docetaxel combination treatment over single-agent docetaxel treatment, as the HRs for all subgroups evaluated were less than 1.00 (Figure 1a). Consistent results across subgroup analyses favoring single-agent docetaxel treatment over single-agent vintafolide treatment were also observed (Figure 1b).



*ADENO. means ADENOCARCINOMA/ADENOSQUAMOUS CARCINOMA/ADENOCARCINOMA WITH OTHER NSCLC VARIANTS

Figure 1a Progression-free Survival Forest Plot: Vintafolide+Docetaxel vs Single-agent Docetaxel

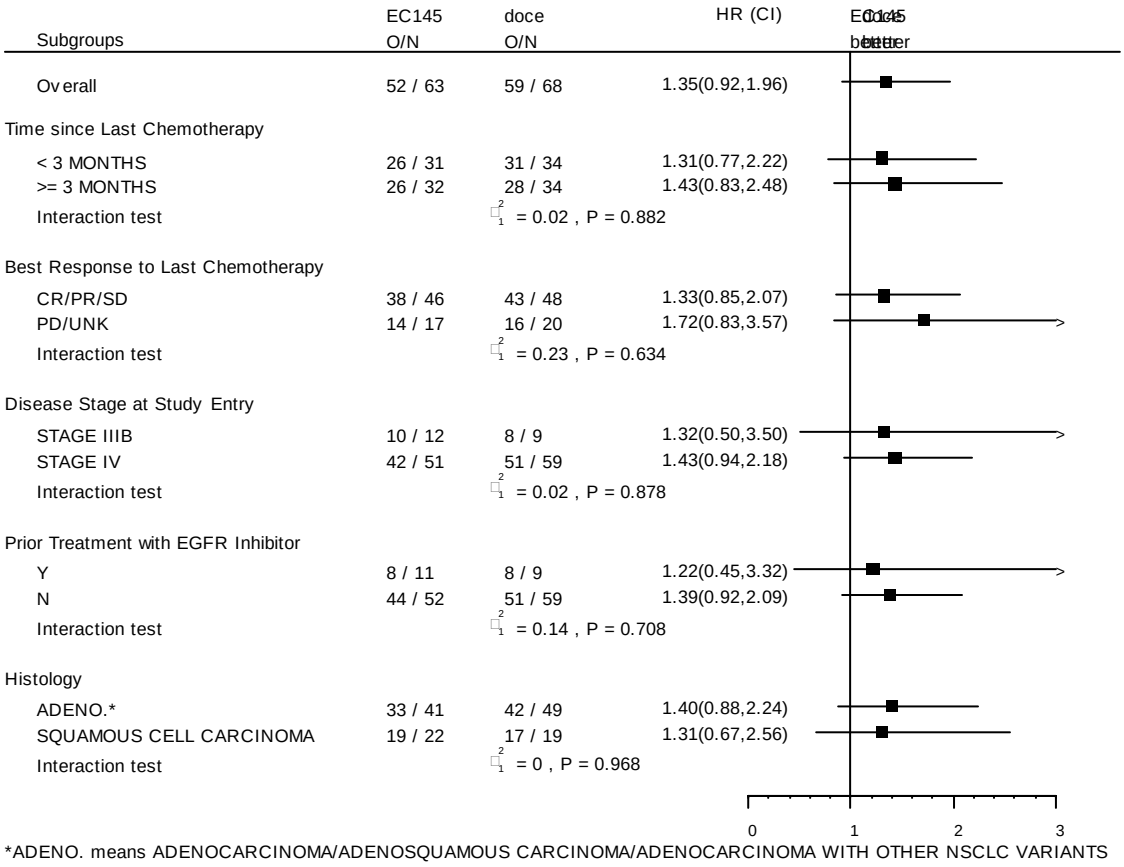


Figure 1b Progression-free Survival Forest Plot: Single-agent Vintafolide vs Single-agent Docetaxel

Secondary Efficacy Results

Both ORR and DCR were higher among patients in the vintafolide+docetaxel combination treatment arm (22.1% and 70.6%, respectively) than among patients in the single-agent docetaxel treatment arm (13.2% and 60.3%, respectively). Overall response rate and DCR were higher among patients treated with single-agent docetaxel than among patients treated with single-agent vintafolide (6.3% and 41.3%, respectively).

Median duration of response was longer in patients in the vintafolide+docetaxel combination treatment arm (4.2 months) than in patients in the single-agent docetaxel treatment arm (3.7 months). Median duration of disease control was similar among patients in the vintafolide+docetaxel combination treatment arm (5.4 months) and patients in the single-agent docetaxel treatment arm (5.5 months); both were longer than median duration of disease control in the single-agent vintafolide treatment arm (4.2 months).

At the time of database lock on 14 February 2014, a total of 92 deaths had occurred and 107 patients (53.8%) were censored for the OS analysis. Median OS was 9.5 months in the single-agent vintafolide treatment arm and 8.8 months in the single-agent docetaxel treatment arm; median OS was not reached in the vintafolide+docetaxel combination treatment arm. Given the relative immaturity of the OS data, firm conclusions cannot be drawn at this time but these preliminary results show that there does not appear to be a detrimental effect of vintafolide treatment on OS in either the single-agent vintafolide treatment arm or the vintafolide+docetaxel combination treatment arm.

Efficacy Results by Histology

When analyzed by histology, there was no difference in PFS between the adenocarcinoma (and its variants) and squamous cell carcinoma subtypes in the vintafolide+docetaxel combination treatment arm, with a median PFS of 4.2 months in both subtypes. There was, however, a statistically significant improvement in PFS in the vintafolide+docetaxel combination treatment arm (median: 4.2 months) compared to the single-agent docetaxel treatment arm (median: 3.0 months) among the 133 patients with adenocarcinoma and its variants (HR: 0.73, 95% CI: 0.46, 1.16; 1-sided p-value by un-stratified log-rank test: 0.0899; Table 5). There was essentially no difference in PFS between the vintafolide+docetaxel combination treatment arm (median: 4.2 months) and the single-agent docetaxel treatment arm (median: 4.0 months) among the 66 patients with squamous cell carcinoma (HR: 0.87, 95% CI: 0.46, 1.66; 1-sided p-value by unstratified log-rank test: 0.3446). Results also suggest a trend in PFS that favors single-agent docetaxel over single-agent vintafolide treatment, regardless of histologic subtype.

The ORRs in the vintafolide+docetaxel combination treatment arm were also similar in the 2 histology subtypes, and were higher than those observed in the single-agent docetaxel treatment arm. The OS results are too immature to make any conclusions regarding subtype results at this time.

Table 5 Primary and Secondary Efficacy Analyses Results by Histology

	Single-agent Vintafolide N=63	Vintafolide+ Docetaxel N=68	Single-agent Docetaxel N=68
ADENOCARCINOMA/ADENOSQUAMOUS CARCINOMA/ADENOCARCINOMA WITH OTHER NSCLC VARIANTS	**41**	**43**	**49**
Median PFS, months (95% CI)	1.6 (1.4, 3.3)	4.2 (2.6, 5.4)	3.0 (1.6, 4.2)
HR PFS (95% CI; unstratified analysis)	1.40 (0.88, 2.24)	0.73 (0.46, 1.16)	
One-sided p-value	0.0753[a]	0.0899	
Overall Response Rate	2 (4.9%)	9 (20.9%)	7 (14.3%)
Median Duration of Response, months (95% CI)	- (-, -)	4.2 (2.8, -)	4.2 (0.8, -)
Disease Control Rate	17 (41.5%)	28 (65.1%)	28 (57.1%)
Median Duration of Disease Control, months (95% CI)	4.2 (3.2, 5.1)	5.9 (4.2, 8.3)	5.5 (3.5, 6.8)
Median OS, months (95% CI)	8.4 (5.1, -)	10.9 (7.6, -)	6.4 (4.8, -)
HR OS (95% CI; unstratified analysis)	0.96 (0.54, 1.70)	0.60 (0.32, 1.14)	
One-sided p-value	0.4432	0.0573	
SQUAMOUS CELL CARCINOMA	**22**	**25**	**19**
Median PFS, months (95% CI)	1.6 (1.3, 2.9)	4.2 (2.6, 5.6)	4.0 (1.4, 5.8)
HR PFS (95% CI; unstratified analysis)	1.31 (0.67, 2.56)	0.87 (0.46, 1.66)	
One-sided p-value	0.2099[a]	0.3446	
Overall Response Rate	2 (9.1%)	6 (24.0%)	2 (10.5%)
Median Duration of Response, months (95% CI)	- (4.4, -)	4.1 (1.4, -)	2.0 (1.4, 2.6)
Disease Control Rate	9 (40.9%)	20 (80.0%)	13 (68.4%)
Median Duration of Disease Control, months (95% CI)	4.6 (1.9, 9.7)	5.4 (3.1, 6.7)	4.3 (3.7, 6.8)
Median OS, months (95% CI)	- (2.9, -)	7.3 (3.5, -)	9.0 (6.3, -)
HR OS (95% CI; unstratified analysis)	1.09 (0.42, 2.84)	1.29 (0.53, 3.17)	
One-sided p-value	0.4271[a]	0.2876[a]	

[a] In favor of the single-agent docetaxel treatment arm.

Safety

Vintafolide and Docetaxel Treatment Administration

Of the 203 randomized patients, 199 patients received at least 1 dose of vintafolide and/or docetaxel and were included in the safety analysis population.

In the single-agent vintafolide treatment arm (n=63), the median number of cycles was 2.0 (range: 1-19 cycles; Table 6). The majority of patients in this arm tolerated treatment well, requiring no treatment interruption or dose reduction. Less than 50% of treatment modifications were due to adverse events. The 1 patient in the single-agent vintafolide treatment arm treated with G-CSF support received 6 cycles of vintafolide; no dose interruptions or reductions were seen.

In the vintafolide+docetaxel combination treatment arm (n=68), the median number of cycles was 4.0 (range: 1-19 cycles) for each treatment. Over 75% of patients required at least 1 vintafolide dose interruption in this treatment arm; most interruptions were due to adverse events, most commonly neutropenia, febrile neutropenia, and pyrexia. Less than one third of patients experienced a vintafolide dose reduction; most dose reductions were due to hematologic toxicities. Less than 15% of patients required a docetaxel dose interruption; the interruption was due to

adverse events (peripheral sensory neuropathy, neutropenic sepsis, infusion-related reaction, and muscular weakness) in 60% of these patients. Just over 50% of patients experienced a docetaxel dose reduction; most were due to hematologic toxicities. In patients who had received G-CSF support (n=37), the median number of treatment cycles was 5.0 for each treatment. Dose interruptions of vintafolide were observed in 34 patients and dose adjustments were observed in 9 patients. Dose interruptions of docetaxel were observed in 7 patients and dose adjustments were observed in 22 patients.

In the single-agent docetaxel treatment arm (n=68), the median number of cycles was 4.0 (range: 1-16 cycles). None of the patients experienced a dose interruption. Twenty-four patients required a dose reduction; most were due to hematologic toxicities. In patients who had received G-CSF support (n=26), the median number of treatment cycles was 5.5. No dose interruptions were observed; dose adjustments were observed in 9 patients.

Table 6 Vintafolide and Docetaxel Administration

	Single-agent Vintafolide N=63	**Vintafolide+ Docetaxel N=68**		**Single-agent Docetaxel N=68**
	Vintafolide	**Vintafolide**	**Docetaxel**	**Docetaxel**
Median number of treatment cycles, n	**2.0**	**4.0**	**4.0**	**4.0**
Range, n	1-19	1-19	1-19	1-16
Total number of treatment cycles, n	**249**	**382**	**349**	**342**
Number of patients with at least:				
One dose interruption, n (%)	**14 (22.2%)**	**55 (80.9%)**	**10 (14.7%)**	**-**
Reason for interruption[a]:				
Adverse event[b], n (%)	6 (42.9%)	50 (90.9%)	6 (60.0%)	-
Other, n (%)	9 (64.3%)	15 (27.3%)	5 (50.0%)	-
One dose adjustment, n (%)	**2 (3.2%)**	**20 (29.4%)**	**35 (51.5%)**	**24 (35.3%)**
Reason for adjustment[a]:				
Prior reduction maintained, n (%)	2 (100%)	20 (100%)	25 (71.4%)	14 (58.3%)
Hematologic toxicity, n (%)	1 (50.0%)	17 (85.0%)	27 (77.1%)	17 (70.8%)
Nonhematologic toxicity, n (%)	1 (50.0%)	3 (15.0%)	11 (31.4%)	7 (29.2%)
Other	-	-	-	1 (4.2%)
Mean (SD) cumulative dose, mg	**37.9 (34.78)**	**44.6 (35.74)**	**642.5 (514.72)**	**662.5 (451.59)**
Median cumulative dose, mg	**20.0**	**40.0**	**527.4**	**536.8**
Mean (SD) dose intensity[c]	**0.4 (0.07)**	**0.3 (0.09)**	**3.0 (0.68)**	**3.3 (0.42)**
Mean (SD) relative dose intensity, %	**94.6 (11.54)**	**73.8 (16.88)**	**83.8 (18.96)**	**92.0 (11.61)**

[a] More than 1 reason may be listed per patient.
[b] Regardless of relatedness.
[c] Dose intensity is measured in mg/day for vintafolide and mg/m^2/day for docetaxel.

Vintafolide and Docetaxel Safety

An overall summary of safety results is presented in Table 7.

Table 7 Overview of Treatment-emergent Adverse Events

	Single-agent Vintafolide N=63	Vintafolide+ Docetaxel N=68	Single-agent Docetaxel N=68	All N=199
Number of patients who experienced at least one:				
Treatment-emergent adverse event, n (%)	54 (85.7%)	67 (98.5%)	65 (95.6%)	186 (93.5%)
Treatment-related[a] TEAE, n (%)	35 (55.6%)	63 (92.6%)	63 (92.6%)	161 (80.9%)
TEAE leading to vintafolide discontinuation, n (%)	2 (3.2%)	7 (10.3%)	-	9 (4.5%)
TEAE leading to docetaxel discontinuation, n (%)	-	10 (14.7%)	4 (5.9%)	14 (7.0%)
Grade ≥3 TEAE, n (%)	25 (39.7%)	62 (91.2%)	56 (82.4%)	143 (71.9%)
Treatment-related[a] Grade ≥3 TEAE, n (%)	10 (15.9%)	57 (83.8%)	51 (75.0%)	118 (59.3%)
Serious TEAE, n (%)	14 (22.2%)	29 (42.6%)	24 (35.3%)	67 (33.7%)
Treatment-related[a] serious TEAE, n (%)	4 (6.3%)	21 (30.9%)	14 (20.6%)	39 (19.6%)
Fatal TEAE, n (%)	5 (7.9%)	6 (8.8%)	6 (8.8%)	17 (8.5%)
Treatment-related[a] fatal TEAE, n (%)	-	1 (1.5%)	2 (2.9%)	3 (1.5%)

[a] Treatment-related events included all events deemed "possibly", "probably", or "definitely" related to study treatment or where relatedness was missing.

- A total of 186 patients experienced at least 1 treatment-emergent adverse event (TEAE) during the study. TEAEs occurring in >10% of patients overall included: neutropenia, fatigue, anemia, peripheral sensory neuropathy, leukopenia, asthenia, diarrhea, decreased appetite, nausea, stomatitis, dyspnea, alopecia, arthralgia, constipation, and vomiting. Overall, more patients in the vintafolide+docetaxel combination treatment and single-agent docetaxel treatment arms experienced neutropenia, leukopenia, febrile neutropenia, diarrhea, nausea, stomatitis, vomiting, fatigue, pyrexia, and alopecia. More patients in the combination treatment arm experienced neutropenia, asthenia, decreased appetite, and peripheral sensory neuropathy than in the single-agent docetaxel treatment arm.
- A total of 161 patients experienced at least 1 TEAE that was deemed related to study treatment (35 patients in the single-agent vintafolide treatment arm, and 63 patients each in the vintafolide+docetaxel and single-agent docetaxel treatment arms):
  - The most common treatment-related TEAEs in the single-agent vintafolide treatment arm were anemia (14.3%), constipation (12.7%), and peripheral sensory neuropathy (12.7%).
  - The most common treatment-related TEAEs in the vintafolide+docetaxel combination treatment arm were neutropenia (73.5%), peripheral sensory neuropathy (27.9%), and leukopenia (25.0%).
  - The most common treatment-related TEAEs in the single-agent docetaxel treatment arm were neutropenia (57.4%), leukopenia (30.9%), and fatigue (27.9%).
- TEAEs that led to study treatment discontinuation occurred in 2 patients in the single-agent vintafolide treatment arm, 10 patients in the vintafolide+docetaxel combination treatment arm (7 of who discontinued both vintafolide and docetaxel and 3 of who discontinued docetaxel only), and 4 patients in the single-agent docetaxel treatment arm.
- A total of 67 patients experienced at least 1 serious TEAE during the study (14 patients in the single-agent vintafolide treatment arm experienced a total of 17 serious TEAEs, 29 patients in the vintafolide+docetaxel combination treatment arm experienced a total of 61 serious TEAEs, and 24 patients in the single-agent docetaxel treatment arm experienced a total of 39 serious TEAEs):
  - The most common serious TEAE in the single-agent vintafolide treatment arm was hemoptysis (4.8%).
  - The most common serious TEAEs in the vintafolide+docetaxel combination treatment arm were febrile neutropenia (11.8%) and neutropenia (11.8%).
  - The most common serious TEAEs in the single-agent docetaxel treatment arm were febrile neutropenia (5.9%), neutropenia (4.4%), and anemia (4.4%).

- A total of 39 patients experienced at least 1 serious TEAE that was deemed related to study treatment (4 patients in the single-agent vintafolide treatment arm experienced a total of 5 treatment-related serious TEAEs, 21 patients in the vintafolide+docetaxel combination treatment arm experienced a total of 36 treatment-related serious TEAEs, and 14 patients in the single-agent docetaxel treatment arm experienced a total of 18 treatment-related serious TEAEs):
  - The treatment-related serious TEAEs in the single-agent vintafolide treatment arm were abdominal pain, atrial fibrillation, hydronephrosis, renal impairment, and ventricular tachycardia.
  - Febrile neutropenia (11.8%) and neutropenia (11.8%) were the most common treatment-related serious TEAEs in the vintafolide+docetaxel combination treatment arm.
  - Febrile neutropenia (5.9%) and neutropenia (4.4%) were also the most common treatment-related serious TEAEs in the single-agent docetaxel treatment arm.
- A total of 118 patients experienced at least 1 treatment-related TEAE that was Grade ≥3 (10 patients in the single-agent vintafolide treatment arm experienced a total of 12 treatment-related Grade ≥3 TEAEs, 57 patients in the vintafolide+docetaxel combination treatment arm experienced a total of 106 treatment-related Grade ≥3 TEAEs, and 51 patients in the single-agent docetaxel treatment arm experienced a total of 83 treatment-related Grade ≥3 TEAEs):
  - The most common treatment-related Grade ≥3 TEAE in the single-agent vintafolide treatment arm was anemia (3.2%).
  - The most common treatment-related Grade ≥3 TEAEs in the vintafolide+docetaxel combination treatment arm were neutropenia (69.1%), leukopenia (17.6%), and febrile neutropenia (13.2%).
  - The most common treatment-related Grade ≥3 TEAEs in the single-agent docetaxel treatment arm were neutropenia (50.0%) and leukopenia (25.0%).
  - Three patients died due to treatment-related TEAEs: 1 patient in the vintafolide+docetaxel combination treatment arm died due to neutropenic sepsis; and 2 patients in the single-agent docetaxel treatment arm died due to sepsis and its complications.
- A total of 92 patient deaths were reported during the study:
  - 31 deaths occurred in the single-agent vintafolide treatment arm; the primary cause of death was considered disease progression in 26 patients, adverse event in 4 patients, and was unknown in 1 patient.
  - 27 deaths occurred in the vintafolide+docetaxel combination treatment arm; the primary cause of death was considered disease progression in 21 patients, adverse event in 5 patients, and was unknown in 1 patient.
  - 34 deaths occurred in the single-agent docetaxel treatment arm; the primary cause of death was considered disease progression in 28 patients, adverse event in 5 patients, and other in 1 patient.

  Note: For 1 patient in each treatment arm who had experienced a fatal TEAE, the primary cause of death was considered disease progression and not the fatal TEAE.
- Most of the serum chemistry and hematology abnormalities observed in the study were Grade 1 or 2 in severity.

Etarfolatide Safety

A total of 290 patients received ^{99m}Tc-etarfolatide (203 were later randomized to study treatment and 87 were never randomized). No ^{99m}Tc-etarfolatide-emergent AEs occurred in ≥ 2% of patients in any treatment arm. A total of 7 ^{99m}Tc-etarfolatide-emergent AEs occurred in 5 patients: anemia, dyspnea, elevated alkaline phosphatase, elevated serum creatinine, fatigue, pyrexia, and vomiting. A total of 289 patients received folic acid. No folic acid-emergent AEs were recorded in this study.

Conclusions:

Overall, efficacy results of this randomized Phase 2 study demonstrate superior outcomes with the combination of vintafolide+docetaxel compared to single-agent docetaxel in the treatment of patients with advanced FR(100%) previously treated NSCLC. The primary PFS efficacy results were consistent across all subgroup analyses and sensitivity analyses showed no sign of systematic bias. On the other hand, PFS, ORR, and DCR endpoint results indicated that treatment with single-agent vintafolide is inferior to treatment with single-agent docetaxel.

When analyzed by histology, no differences in PFS or ORR results were observed between the adenocarcinoma (and its variants) and squamous cell carcinoma subtypes in the vintafolide+docetaxel combination treatment arm. In the single-agent docetaxel treatment arm, patients with adenocarcinoma (and its variants) had a shorter PFS than patients with squamous cell carcinoma but there was no difference in ORR results between the 2 histology subtypes. As a result, the greatest PFS benefit of the combination treatment over single-agent docetaxel was observed in patients with adenocarcinoma (and its variants).

Single-agent vintafolide treatment had a more favorable toxicity profile than single-agent docetaxel treatment, with minimal hematologic and nonhematologic toxicities. On the other hand, neutropenia, febrile neutropenia, and peripheral sensory neuropathy were more common in the vintafolide+docetaxel combination treatment arm compared to the single-agent docetaxel treatment arm. The increased toxicity observed with vintafolide+docetaxel combination treatment in this study was offset by increased efficacy leading to a favorable risk/benefit profile of the combination compared to single-agent docetaxel. All study treatments/agents (i.e., single-agent vintafolide, vintafolide+docetaxel, single-agent docetaxel, and ^{99m}Tc-etarfolatide) were generally well tolerated and manageable.