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Sponsor / Company: Sanofi **Drug substance(s):** Docetaxel (Taxotere®)	**Study Identifiers:** NCT01038661 **Study code:** DOCET_L_04827
Title of the study: Randomized, Controlled Study Comparing the Efficacy and Safety of Docetaxel (60 mg/m^2) Maintenance Treatment vs. Best Supportive Care Following First Line Chemotherapy with Different Doses of Docetaxel (75/60 mg/m^2) in combination with Cisplatin in Patients with Local Advanced or Metastatic (Stage IIIB/IV) Non-Small Cell Lung Cancer	
Study center(s): 15 actives sites in China	
Study period: Date first patient enrolled: 03/Nov/2009 Date last patient completed: 31/Aug/2012	
Phase of development: Phase III	

Objectives:

Primary objective:

- Progression-free survival (PFS): To calculate the PFS since entering maintenance treatment after second randomization to the date of progression or death of any cause (whichever occurred first)

Secondary objectives:

- To compare the disease control rate (DCR＝CR+PR+SD) with different dose docetaxel (75 mg/m^2/60 mg/m^2) plus cisplatin during first line treatment as assessed by RECIST 1.0
- To compare the objective response rate (ORR＝CR+PR) with different dose docetaxel (75 mg/m^2/60 mg/m^2) plus cisplatin during first line treatment as assessed by RECIST 1.0
- Time to progression (TTP): To calculate the TTP since entering maintenance treatment after second randomization to the date of progression
- Overall survival (OS): To calculate the OS from first randomization to the date of death from any causes
- Safety assessment (using NCI CTCAE V3.0)
- The following were analyzed for the safety of treatment: adverse events (AEs), vital signs (blood pressure, heart rate, and body temperature) and laboratory tests, etc.

Exploratory objective:

- To detect the CYP3A4 (cytochrome P450) genotype difference in peripheral venous blood, exploring its correlation with safety/efficacy indicators

Methodology:

This was a multicenter, controlled, dynamic randomized study to compare the efficacy and safety of docetaxel (60 mg/m^2) as maintenance treatment versus best supportive care (BSC), and compare the efficacy and safety of different doses of docetaxel (75/60 mg/m^2) plus cisplatin as the first-line setting in patients with local advanced or metastatic (Stage IIIB/IV) non-small-cell lung cancer (NSCLC).

Patients received a maximum 4 cycles of chemotherapy at 3 week intervals unless disease progression/relapse (hereafter, progression) or unacceptable toxicity occurred, or the patient refused treatment. Patients with disease control after the initial treatment were subsequently randomized (1:2) to BSC or maintenance docetaxel of 60 mg/m^2 for up to 6 cycles. Genomic DNA was prospectively collected from all enrolled patients.

Number of patients: Planned: 380

Randomized: 375

Treated: 374

Evaluated:

Efficacy: 374

Safety: 374

Diagnosis and criteria for inclusion:

1. Cytologically or histologically confirmed NSCLC (simple diagnosis by sputum cytologic examination was not acceptable)
2. Stage IIIB or IV NSCLC as assessed by International Association for the Study of Lung Cancer (IASLC) 2009 new Tumor-Node-Metastasis (TNM) staging criteria of lung cancer
3. Patients with at least 1 measurable lesion (longest diameter ≥10 mm on spiral computed tomography [CT] scan or ≥20 mm using conventional techniques) by RECIST 1.0
4. Male or female aged ≥18 years and ≤75 years
5. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1
6. Life expectancy ≥12 weeks
7. Adequate hematologic function: absolute neutrophil count (ANC) ≥2×10^9/L; platelet count ≥100×10^9/L; and hemoglobin ≥9 g/dL
8. Adequate liver function: total bilirubin ≤1×ULN; aspartate amino transferase (AST) and alanine amino transferase (ALT) ≤2.5×ULN; alkaline phosphatase (ALP) ≤5×ULN
9. Adequate kidney function: serum creatinine ≤1×ULN or calculated creatinine clearance (Ccr) ≥60 mL/min
10. Patient previously untreated with anti-tumor drug therapy, or only treated with adjuvant or neoadjuvant therapy (pies) for nonmetastatic tumor(s), which must have been stopped for over 6 months at the commencement of study treatment (the cumulative previous cisplatin dose should not exceed (350 mg/m^2)
11. For patient who previously received surgery, the surgery must have been completed for over 4 weeks and the patient has recovered
12. Women with intact uterus must have negative pregnancy test within 28 days prior to study enrollment (unless postmenopausal for at least 24 months). If the pregnancy test was done over 7 days apart from the first dose, it was required to be confirmed by a urine pregnancy test within 7 days prior to first dose.
13. Written informed consent form (the Informed Consent Form was required to be approved by the Independent Ethics Committee and must be obtained before starting any study procedure).

Study treatments

Investigational medicinal product(s): Docetaxel

Formulation: 20 mg / 80 mg for intravenous infusion

Route(s) of administration: Intravenous

Dose regimen:

At initially randomized (R1), enrolled patients were assigned 1:1 to receive treatment with either docetaxel (75 mg/m^2) plus cisplatin (75 mg/m^2) (Group A); or docetaxel (60 mg/m^2) plus cisplatin (75 mg/m^2) (Group B) given as infusions at Day 1 of each 3-week cycles for 4 cycles.

Patients with disease control (complete response [CR], partial response [PR] or stable disease [SD]) after the initial treatment were subsequently randomized (R2, 1:2) to BSC or maintenance docetaxel group.

Group AB1 to receive BSC until progressive disease (PD), with subsequent treatment (second or third line) at the discretion of the investigator, or

Group AB2 to receive docetaxel (60 mg/m^2) given as infusions at Day 1 of each 3-week cycles until PD or for up to 6 cycles.

Duration of treatment:

The treatment was to be started within 7 days following randomization and continued until PD, intolerable toxicity, death, patient's voluntary discontinuation or loss to follow-up. In the first line treatment phase, patients were to receive 4 cycles of chemotherapy (each cycle contains 3 weeks), followed by the second randomization within one week following the end of the last cycle of the first line treatment. The maintenance treatment phase was to start within one week following the second randomization and patients could receive up to 6 cycles of chemotherapy. The estimated duration of study treatment was therefore about 32 weeks.

Duration of observation:

The follow-up period starts from the end of study treatment and continues until patient death or end of study. During this period, patients were to be routinely followed up every 8 weeks for knowledge and documentation of survival and subsequent anti-tumor therapies. In addition, for patients without disease progression at the end of study treatment, tumor response was to be assessed and survival was to be followed up at the interval of every 6 weeks until disease progression or receiving other anti-tumor therapies. Once disease progression or subsequent anti-tumor therapy is confirmed, survival was to be followed up at the interval of every 8 weeks.

Criteria for evaluation:

Efficacy: Primary efficacy data was the PFS since entering maintenance treatment after second randomization to the date of progression or death of any cause (whichever occurred first).

Secondary efficacy data included the DCR (CR+PR+SD) and the ORR (CR+PR) during the first line treatment, also included the TTP since entering maintenance treatment after second randomization to the date of progression and the OS after first randomization to the date of death from any cause.

Safety: AEs reported by the patient or noted by the investigator. All AEs will be graded by National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) V3.0, and reference CRF detailed content.

Exploratory: To detect the CYP3A4 (cytochrome P450) genotype difference in peripheral venous blood, exploring its correlation with safety/efficacy indicators.

Statistical methods:

Sample size determination:

Assuming a 50% improvement of PFS (3 month in BSC group versus 4.5 months in the maintenance group) would indicate superiority over BSC group, at α=0.05, β=0.2, with 2:1 randomization, for an enrollment period of 18 months and a follow-up of 24 months, an estimated sample size of 270 patients (180 in the maintenance group and 90 in the BSC group) was expected to be required.

Considering the 20% chance of PD in patients who have received 4 cycles of docetaxel plus cisplatin and the estimated drop-out rate of 10%, a total sample size of 380 patients was expected to be required.

Analysis populations:

Due to 2 times randomizations in the study, the analysis populations have two subdivisions separately as follows, see Table 1:

Table 1 the subdivision of analysis population

Analysis population	Abbreviation	First-line treatment	Maintenance treatment
Intent to treat population	ITT	ITT-1	ITT-2
Evaluable population	EP	EP-1	EP-2
Safety population	SP	SP-1	SP-2

Efficacy analysis:

The primary analysis:

The primary analysis was to compare PFS in the intention-to-treat population 2 (ITT-2) using Cox proportional hazards model. The model was fit with factors include the second randomization factors, a 2-sided 0.05 significance level was applied to the estimate of the treatment hazard ratio and its 95% confidence interval (CI). The median PFS, the difference of median PFS between two groups and its 95% CI was estimated by Kaplan-Meier method. Kaplan-Meier curve was presented. Log-Rank Test was used to test the difference between two treatment groups.

Overall PFS was compared in the intention to treat population 1 (ITT-1) and evaluable population 1 (EP-1) using the same analysis method mentioned above (Cox proportional hazards model, Kaplan-Meier method and Log-Rank test), while the Cox proportional hazards model was fit with factors include the first randomization factors.

Descriptive statistics of overall PFS for subgroups after the second randomization was presented.

Secondary efficacy analysis:

Secondary efficacy analyses were to compare DCR in the ITT-1 and EP-1 populations, a non-inferiority test with a non-inferiority margin of -15% was used, and conclusion is depended on the result in evaluable population.

ORR was compared by Chi-square test (Fisher's exact test if the frequency of any variable in the contingency table is <5) between groups in the ITT-1 and EP-1 populations.

The same methods applied for primary analysis (Cox proportional hazards model, Kaplan-Meier method and Log-Rank test) were used to compare TTF in the ITT-2 and EP-2 populations, while the Cox model was fit with factors include the second randomization factors.

The same methods applied for primary analysis were used to compare OS in the ITT-1 and EP-1 populations, while the Cox model was fit with factors include the first randomization factors.

A 0.05 significance level was applied to all tests.

Safety analysis:

Safety analyses were performed in safety population. The safety profile of the experimental group was compared to the control group using the NCI-CTCAE V3.0 criteria.

Descriptive statistics were presented for overview of AEs, the incidence of AEs, relationship of AEs associated with experimental drug, severity of AEs and serious adverse events (SAEs).

Pharmacodynamics variable analysis

Pharmacodynamics variable analysis was to analyze the relationship of genotype differences associated with PFS or other efficacy/safety indicators in disease progression.

Primary efficacy PFS/overall PFS/OS was compared by Cox proportional hazards model between two groups with different genotypes, with the hazard ratio (HR) and its 95% CI between groups estimated, respectively.

The distribution of DCR/ORR was compared by Chi-square test (Fisher's exact test if the frequency of any variable in the contingency table is <5) between two groups with different genotypes in first line treatment period.

The incidence of AEs, SAEs and severe adverse events (NCI-CTCAE ≥3) was compared by Chi-square test (Fisher's exact test if the frequency of any variable in the contingency table is <5) between two groups with different genotypes in first line treatment period and maintenance treatment period.

Logistic regression model was used to estimate the association of genotype difference with the following events: DCR, ORR and AEs, respectively. The model was fit with gender, pathological classification (Squamous vs. Non-squamous) and dose of docetaxel used in first line treatment period. Odds ratios of genotype to different event and its 95% confidence interval were estimated by both the fitted model and the model without fit.

A 0.05 significance level was applied to all tests.

Summary:

Population and demographic characteristics: A total of 375 patients were initially randomized from 15 centers as the ITT-1 population; 374 patients were treated and entered into the safety population-1 (SP-1); 314 patients were included into the EP-1 population, and only 1 was ruled out for having not received any treatment. All of the other 374 patients received the study treatment as they were randomized to.

A total of 184 patients with disease control after the initial treatment were subsequently randomized as the ITT-2 population; 179 patients were included in the safety population-2 (SP-2); 154 patients were included in the EP-2 population. A total of 5 patients were randomized but never treated. All 179 patients received the study treatment to which they were randomized.

The table below presents the reasons for chemotherapy discontinuation in the ITT-1 and 2 populations, and it was similar between the A group and the B group.

Table 2 The reasons for chemotherapy discontinuation (ITT-1 and ITT-2)

Number (%) of patients	B group	A group	All
	Docetaxel 60 mg/m^2	Docetaxel 75 mg/m^2	
ITT-1	188	187	375
EP-1	155 (82.4)	159 (85.0)	314 (83.7)
SP-1	188 (100.0)	186 (99.5)	374 (99.7)
ITT-2	90 (47.9)	94 (50.3)	184 (49.1)
EP-2	74 (39.4)	80 (42.8)	154 (41.1)
SP-2	87 (46.3)	92 (49.2)	179 (47.7)
Primary reason for discontinuation			
Adverse events	0	0	0
Death	137 (72.9)	139 (74.3)	276 (73.6)
Progressive disease	0	0	0
Patient's request of protocol prohibited treatment	0	0	0
Major protocol violation	0	0	0
Consent withdrawn	4 (2.1)	6 (3.2)	10 (2.7)
Lost to follow-up	16 (8.5)	23 (12.3)	39 (10.4)

Information on chemotherapy in the SP-1&2 populations, which consisted of all 374 treated patients (SP-1) and 179 treated patients (SP-2), respectively is summarized in the tables below. The 2 treatment groups during the first line treatment were comparable with respect to study treatment delivery and duration.

Table 3 Delivery and duration of study treatment (SP-1)

	B group Docetaxel 60 mg/m^2	A group Docetaxel 75 mg/m^2
	(N=188)	(N=186)
No. of patients who received chemotherapy	188	186
Median duration of chemotherapy (weeks)	12.1	12.1
Relative dose intensity of chemotherapy	96.9%	96.3%
No. of cycles received	607	620
Median No. of cycles by patient	4	4
No. of patients (%) completed chemotherapy as per protocol	128 (68.1%)	133 (71.5%)

Table 4 Delivery and duration of study treatment (SP-2)

	AB2 group Docetaxel	AB1 group BSC
	(N=118)	(N=61)
No. of patients who received chemotherapy	118	0
Median duration of chemotherapy (weeks)	11.4	0
Relative dose intensity of chemotherapy	97.1%	0
No. of cycles received	434	0
Median No. of cycles by patient	3.7	0
No. of patients (%) completed chemotherapy as per protocol	40 (33.9%)	0

Demographics and baseline characteristics of ITT-1&2 populations are summarized in the tables below, respectively. The 2 treatment groups were comparable with respect to demographics and tumor characteristics at baseline.

Table 5 Demographics and Baseline Characteristics (ITT-1)

	B group Docetaxel 60 mg/m^2	A Group Docetaxel 75 mg/m^2
	(n,%) N=188	(n,%) N=186
Age	56 (27, 75)	56 (24,74)
Gender		
Male	122 (64.9)	120 (64.5)
Female	66 (35.1)	66 (35.5)
Disease stage		
IIIB	29 (15.4)	34 (18.3)
IV	159 (84.6)	152 (81.7)
Smoking status		
smoker	76 (40.4)	91 (48.9)
Never-smoker	112 (59.6)	95 (51.1)
ECOG Performance status		
0	67 (35.6)	56 (30.1)
1	121 (64.4)	130 (69.9)
Histology		
Squamous	53 (28.2)	58 (31.2)
Adenocarcinoma	125 (66.5)	109 (58.6)
Large Cell	1 (0.5)	2 (1.1)
Other or indeterminate	9 (4.8)	17 (9.1)

Table 6 Demographics and Baseline Characteristics (ITT-2)

	AB2 group Docetaxel (n,%) N=118	AB1 group BSC (n,%) N=61
Age	55 (33, 71)	57 (39, 75)
Gender		
Male	73 (61.9)	40 (65.6)
Female	45 (38.1)	21 (34.4)
Disease stage		
IIIB	14 (11.9)	16 (26.2)
IV	104 (88.1)	45 (73.8)
Smoking status		
smoker	62 (52.5)	33 (54.1)
never-smoker	56 (47.5)	28 (45.9)
ECOG Performance status		
0	41 (34.7)	18 (29.5)
1	77 (65.3)	43 (70.5)
Histology		
Squamous	35 (29.7)	17 (27.9)
Adenocarcinoma	78 (66.1)	40 (65.6)
Large Cell	1 (0.8)	0
Other or indeterminate	4 (3.4)	4 (6.6)

Efficacy results:

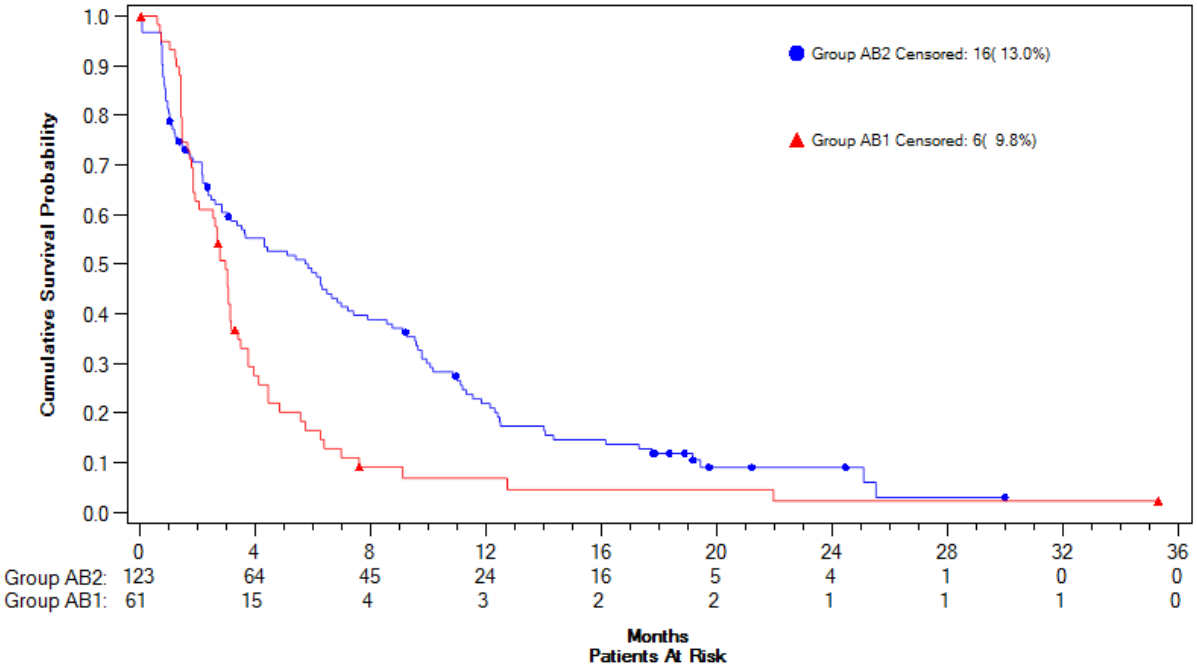
Primary endpoint assessment

The primary efficacy analysis was a comparison of PFS in the ITT-2 population at the end of the study using a Cox proportional hazards model. In the ITT-2 population, the median PFS in the docetaxel (60 mg/m^2) group was 5.8 months (95% CI: 3.2-7.2), the median PFS in the BSC group was 3.0 months (95% CI: 2.0-3.2), and the difference was 2.8 months, see Figure 1. Maintenance docetaxel significantly prolonged PFS compared with BSC (P=0.0022). One year PFS and 2 year PFS estimated by Kaplan-Meier in docetaxel (60 mg/m^2) group were significantly longer than in BSC group.

In the EP-2 population, the median PFS in the docetaxel (60 mg/m^2) group was 6.2 months (95% CI: 3.6-7.8), the median PFS in the BSC group was 3.4 (95% CI: 1.9-3.4), and the difference was 3.4 months. The median PFS was significantly longer in the docetaxel (60 mg/m^2) group than in the BSC group (P=0.0030).

The results of Cox proportional hazards regression analysis demonstrated that in the ITT-2 population, stratification factors adjusted hazard ratio comparing docetaxel (60 mg/m^2) group with BSC group was 0.567 (95%CI: 0.401-0.803), with P value <0.05 (P=0.0012).

Figure 1 Primary Endpoint Progression-Free Survival Kaplan-Meier Curve (ITT-2)



Secondary endpoint assessments

1. Disease control rate (DCR)

In the ITT-1 population, the DCR in the group B was 72.4%, and that in the group A was 78.6%, and the difference of the DCRs between the two groups was –6.3% (95% CI: -14.95%, 2.42%).

In the EP-1 population, the DCR in the group B was 74.8%, and that in the group A was 81.8%, and the difference of the DCRs between the two groups was –7.8% (95% CI: -17.40%, 1.77%).

Taken together the results in the ITT-1 and EP-1 populations, the lower bound of 95% CI for the intergroup DCR difference in the ITT-1 was higher than the noninferiority margin, i.e. 15%, while the lower bound of the 95% CI for the intergroup DCR difference in the EP-1 population was less than the noninferiority margin. In accordance with the protocol of the clinical trial, and the plan of statistical analysis, the results in the EP-1 were used to evaluate the non-inferiority. Therefore, based on the results in the EP-1 population, it was still unable to determine whether docetaxel (60 mg/m^2)/cisplatin was noninferior to docetaxel (75 mg/m^2)/cisplatin in terms of disease control.

2. Objective response rate (ORR)

In the ITT-1 population, the ORRs in the group B and A were 23.9% and 28.3% respectively, and the difference was not statistically significant (Chi square test, P>0.05). The intergroup difference of ORR in the EP-1 population was not significant either.

3. Time to progression (TTP)

In the ITT-2 population, the median TTP of maintenance docetaxel 60 mg/m^2 group was 6.6 months, and BSC group was 3.0 months; the TTP of the docetaxel 60 mg/m^2 group was significantly longer than that of BSC group (P=0.0088).

In the EP-2 population, the PPT of the maintenance docetaxel 60 mg/m^2 group was significantly longer than that of BSC group (P=0.0002).

The stratification factors adjusted hazard ratio (HR) in Cox proportional hazards model comparing maintenance docetaxel 60 mg/m^2 group and the BSC group was 0.571 (95%CI: 0.390,0.836) in the ITT-2 population; the hazard of the docetaxel 60 mg/m^2 group was significantly lower than that of BSC group, P<0.05 (P=0.0040). In the EP-2 population, the hazard ratio comparing docetaxel 60 mg/m^2 group and BSC group was 0.445 (95%CI: 0.297,0.667), the hazard of the docetaxel 60 mg/m^2 group was significantly lower than that of BSC group (P<0.001).

4. Overall survivals (OS)

In the ITT-1 population, the median overall survivals in group B and A were 13.0 months and 11.8 months respectively, and the difference was not significant (P=0.2559).

The results obtained from the EP-1 population was comparable to the ITT-1 population, the intergroup difference was not significant (P=0.2425).

In the ITT-1 and EP-1 populations, stratification factors adjusted hazard ratio of the two groups both involved 1, P>0.05.

Pharmacodynamic variable analysis

The distributions of the 5 polymorphisms and their association with PFS, overall PFS, OS, DCR, and ORR were studied.

Preliminary pharmacogenomic analysis of the association of each polymorphism with PFS, overall PFS and OS demonstrated the CYP3A5*3C (6986 AG/GG) genotype associated with poor PFS.

Preliminary pharmacogenomic analysis of the association of each polymorphism with DCR and ORR demonstrated that SNPs in CYP3A4, CYP3A5 and ABCB1 couldn't predict the DCR or ORR of docetaxel chemotherapy.

The frequencies of the result of logistic regression analysis of some genotypes were considerably low. Hence the results are only for reference.

Safety results:

First-line treatment period (After 1st randomization)

The SP-1 population consisted of 374 patients who received at least 1 dose of study treatment. A summary of the incidence of treatment emergent adverse events (TEAEs) in the SP-1 population is presented in the table below.

Table 7 The summary of TEAEs in the first treatment period (SP-1)

	B group (N=188) n (%) n'	A group (N=186) n (%) n'	Total (N=374) n (%) n'
All adverse event	86 (45.7) 660	89 (47.8) 738	175 (46.8) 1398
Serious adverse event	4 (2.1) 4	7 (3.8) 10	11 (2.9) 14
Severe adverse event, severity (NCI-CTCAE 3.0)	76 (40.4) 250	70 (37.6) 293	146 (39.0) 543
Adverse event related to study treatment	85 (45.2) 604	85 (45.7) 673	170 (45.5) 1277
Serious adverse event related to study treatment	3 (1.6) 3	7 (3.8) 8	10 (2.7) 11
Adverse event lead to study discontinuation	0	2 (1.1) 3	2 (0.5) 3

n = No. of patients

n' = No. of events

A total of 86 patients (45.7%) in docetaxel 60 mg/m^2 group (B group) and 89 patients (47.8%) in docetaxel 75 mg/m^2 group (A group) experience at least 1 AE. Among them, 4 (2.1%) patients in group B and 7 (3.8%) patients in group A were recorded with serious TEAEs. Most TEAEs (around 92%) were related to the chemotherapy in both groups. Two patients in the high dose of docetaxel (75 mg/m^2) group discontinued from the study. There was no death during the first line treatment period.

The frequency of adverse reaction diarrhea was less in low dose of docetaxel (60 mg/m^2) than the high dose of docetaxel (75 mg/m^2) (P=0.029). Other frequencies of clinically important, drug-related TEAE were similar in the 2 groups as shown in the table below:

Table 8 Frequency of Clinically Important, Drug-related TEAE (SP1)

	B group Docetaxel 60 mg/m^2		A group Docetaxel 75 mg/m^2		P	
	Any Grade	**Grade 3or 4**	**Any Grade**	**Grade 3or 4**	**Any Grade**	**Grade 3 or 4**
Hematologic events						
Anemia	53 (28.2)	1 (0.5)	54 (29.0)	0 (0)	0.909	1.000
Neutropenia	117 (62.2)	56 (29.8)	119 (64.0)	58 (31.2)	0.749	0.822
Leucocytopenia	127 (67.6)	35 (18.6)	131 (70.4)	28 (15.1)	0.577	0.408
Thrombocytopenia	13 (6.9)	3 (1.6)	9 (4.8)	0 (0)	0.511	0.248
Febrile neutropenia	1 (0.5)	1 (0.5)	5 (2.7)	2 (1.1)	0.121	0.622
Nonhematologic events						
Nausea	51 (27.1)	1 (0.5)	52 (28.0)	1 (0.5)	0.908	1.000
Vomit	39 (20.7)	3 (1.6)	35 (18.8)	0 (0)	0.698	0.248
Diarrhea	6 (3.2)	1 (0.5)	16 (8.6)	6 (3.2)	0.029	0.067
ALT increased	14 (7.4)	1 (0.5)	9 (4.8)	1 (0.5)	0.390	1.000

Maintenance treatment period (After 2nd randomization)

The SP-2 population consisted of 179 patients. A summary of incidence of TEAEs in the SP-2 population is presented in the table below.

Table 9 The summary of TEAEs in the maintenance treatment period (SP-2)

	AB2 Docetaxel	AB1 BSC	Total
	(N=118) n (%) n'	(N=61) n (%) n'	(N=179) n (%) n'
All adverse event	87 (73.7) 506	7 (11.5) 14	94 (52.5) 520
Serious adverse event	6 (5.1) 8	0	6 (3.4) 8
Severe adverse event, severity (NCI-CTCAE 3.0)	66 (55.9) 183	3 (4.9) 6	69 (38.5) 189
Adverse event related to study treatment	84 (71.2) 454	2 (3.3) 4	86(48.0) 458
Serious adverse event related to study treatment	4 (3.4) 5	0	4 (2.2) 5
Adverse event lead to death	1 (0.8) 1	0	1 (0.6) 1
Adverse event related to study treatment that lead to death	0	0	0
Adverse event lead to study discontinuation	5 (4.2) 7	0	5 (2.8) 7
Adverse event related to study treatment that lead to study discontinuation	4 (3.4) 5	0	4 (2.2) 5

n = No. of patients

n' = No. of events

A total of 87 (73.7%) patients in the docetaxel group (AB2) compared to 7 (11.5%) patients in the BSC group (AB1) experienced at least one AE during the maintenance treatment. Among them, 6 (5.1%) patients in the AB2 group were recorded with SAEs. A total of 90% AEs in AB2 group were related to the docetaxel treatment compared to 43% AEs related to BSC in the AB1 group. Four (3.4%) patients receiving docetaxel treatment discontinued from the study. One patient died during the docetaxel treatment.

Most SAEs in the docetaxel group were intermediate, severe, or life-threatening. Seven patients in BSC group experienced either mild or life-threatening SAEs.

Adverse events were more prevalent in patients receiving docetaxel during the maintenance treatment period included anemia (P<0.001), neutropenia (any grade, grade 3 or 4; P<0.001), and leucocytopenia (any grade, grade 3 or 4; P<0.003) as shown in the table below:

Table 10 Frequency of Clinically Important, Drug-related TEAE (SP-2)

	AB2 group Docetaxel		AB1 group BSC		P	
	Any Grade	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Hematologic events						
Anemia	24 (20.3)		0 (0)		<0.001	
Neutropenia	62 (52.5)	27 (22.9)	2 (3.3)	1 (1.6)	<0.001	<0.001
Leukocytopenia	68 (57.6)	15 (12.7)	1 (1.6)	0 (0)	<0.001	0.003
Febrile neutropenia	2 (1.7)	1 (0.8)	0 (0)	0 (0)	0.548	1.000
Thrombocytopenia	3 (2.5)		0 (0)		0.552	
Nonhematologic events						
Nausea	5 (4.2)		0 (0)		0.168	
Vomiting	2 (1.7)		0 (0)		0.548	
Diarrhea	1 (0.8)		0 (0)		1.000	
ALT increased	6 (5.1)		0 (0)		0.097	

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