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Sponsor: Sanofi	**Study Identifiers:** NCT00995293
Drug substance(s): Docetaxel	**Study code:** DOCET_L_02557
Title of the study: An Open-Label, Randomized, Parallel-Group, Multicenter Study of Neoadjuvant Docetaxel (Taxotere®) plus Cisplatin plus 5-Fluorouracil Versus Neoadjuvant Cisplatin plus 5-Fluorouracil in Patients with Locally Advanced Inoperable Squamous Cell Carcinoma of the Head and Neck	
Study center(s): 15 active sites in China	
Study period: Date first patient enrolled: 27/Aug/2009 Date last patient completed: Not applicable (the cut-off date for this analysis was 31-Jan-2016, 12 months after last patient in)	
Phase of development: 3	
Objectives: **Primary objective:** To evaluate the progression-free survival after treatment with docetaxel (Taxotere®) plus cisplatin plus 5- fluorouracil (TPF) in comparison with cisplatin plus 5- fluorouracil (PF) in patients with locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN). **Secondary objectives:** To evaluate and compare the clinical response rate both before and after radiotherapy, the local symptoms, the duration of response, the time to treatment failure, the survival, the toxicity and the quality of life in the 2 study groups.	
Methodology: This was a randomized, open label, multicenter, registration clinical trial comparing two combination chemotherapy regimens as induction chemotherapy for patients with locally advanced inoperable SCCHN. Patients were randomized to receive either the test triple therapy (TPF) or the control treatment (PF), followed by radiotherapy in both groups. Randomization was centralized and stratified for primary tumor site and center. 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. Chemotherapy was to be followed by radiotherapy for patients who did not have progressive disease. All patients were to be followed up until death. Patients with progression noted at any time were immediately referred to the radiation oncologist according to the center's policy and were followed for survival	

Number of patients:	Planned: 240 Randomized: 239 Treated: 228
Evaluated:	Efficacy: 219 Safety: 228

Diagnosis and criteria for inclusion:

Patients with locally advanced, inoperable, histologically or cytologically proven SCCHN were included in the study after giving written informed consent. Primary tumor sites eligible were: oral cavity, oropharynx, hypopharynx and larynx.

Patients were between 18 and 70 years, and had to have at least one measurable lesion according to RECIST 1.0 standard, TNM stage III or IV without evidence of distant metastases, and WHO performance status (PS) 0 or 1.

Patients had no previous chemotherapy or radiotherapy or surgery for SCCHN, no concurrent treatment with any other anticancer therapy, no chronic treatment (≥ 3 months) with corticosteroids at a daily dose ≥ 20 mg methylprednisolone or equivalent, and no concomitant use of drugs which could interact with 5-fluorouracil (5-FU).

Patients had no previous or current malignancies at other sites with the exception of adequately treated in situ carcinoma of the cervix uteri, basal or squamous cell carcinoma of the skin or other cancer curatively treated by surgery and with no evidence of disease for at least 5 years, no esthesioneurosis ≥ grade 2 by NCI-CTCAE V3.0 criteria, no altered hearing ≥ grade 2, and no other serious illness or medical condition.

Study treatments

Investigational medicinal product(s):

Docetaxel: concentrate for solution (0.5ml:20mg and 2.0ml:80mg) with solvent (13% w/w solution of ethanol in water)

Cisplatin: commercially available in 20 mg vial

5-FU: commercially available in 250 mg vial

Test group (TPF): docetaxel (Taxotere®) (60mg/m^2, 1 hour i.v. infusion on Day 1) →cisplatin (60mg/m^2, 1 hour i.v. infusion on Day 1) →followed by the continuous i.v. infusion of 5-FU 750 mg/m^2/day from Day 1 to Day 5.

Control group (PF): cisplatin 75mg/m^2, 1 hour i.v. infusion on Day 1→followed by the continuous i.v. infusion of 5-FU 750 mg/m^2/day from Day 1 to Day 5.

The cycles were repeated every 3 weeks for at least 3 cycles and up to 4 cycles at most in both treatment groups.

In the TPF treatment group, premedication for Taxotere included dexamethasone and ciproflaxin. In both treatment groups, premedication for cisplatin included hydration and antiemetics (5-HT3 antagonist). Granulocyte colony stimulating factor (G-CSF) was not permitted in the first treatment cycle but was administered prophylactically during the second and/or subsequent cycles if clinically indicated.

In both treatment groups, patients not progressing after chemotherapy received locoregional radiotherapy within 3 to 7 weeks after chemotherapy. Radiation was delivered over 7 weeks using either a conventional fractionation (total dose of 66 to 70 Gray [Gy]) or accelerated/ hyperfractionated regimens of radiation therapy (total dose up to a maximum of 70 Gy for accelerated regimens and a maximum of 74 Gy for hyperfractionated schemes).

Surgery was allowed between chemotherapy and radiotherapy and following radiotherapy, at the discretion of the investigator.

Duration of treatment: Patients was planned to receive a minimum of 3 cycles, no more than 4 cycles of chemotherapy unless progression, unacceptable toxicity or patient refusal. Patients who presented toxicity during chemotherapy or refused chemotherapy should continue radiotherapy according to the protocol unless refusing radiotherapy. Patients with progression noted at any time during the study should be immediately referred to the radiation oncologist. Only patients with progression of

disease should stop study treatment and be treated and followed according to local institutional policies.

Duration of observation: All patients would remain on study until death. Follow-up should continue after end of study treatment every three months for the first year and then every 6 months until death or close of the study. The study would be closed after more than 75% of the patients were dead.

Criteria for evaluation:

Efficacy:

Primary efficacy data was the progression-free survival (PFS). The cut-off date for the primary analysis will be 12 months after the last patient in or later.

Secondary efficacy data included overall response rates (ORR) before and after radiotherapy, duration of response, time to treatment failure (TTF), and overall survival (OS).

Safety:

Safety data included adverse events, clinical examinations, vital signs, weight, neurological examination, PS, ECG, chest-X-ray and laboratory tests (hematology and biochemistry). Clinical and laboratory toxicity/symptom were graded according to NCICTCAE V3.0.

Quality-of-life and clinical benefit:

Quality of life (QoL) was assessed 5 times during the study by the EORTC-QLQ-C30 and the QLQ-H&N35 independently of treatment or disease status. There were 5 primary domains for this trial: global quality of life from the EORTC QLQ-C30 module, and pain, swallowing, speech, and coughing from the QLQ-H&N35 module.

Clinical benefit (local symptoms) data consisted of 3 subscales: the validated performance status scale for head and neck (PSSHN), pain intensity scores from a visual analog scale (VAS), and WHO performance scores

Statistical methods:

Sample size determination

According to the relevant regulations, at least 100 pairs of valid patients were required for a new indication application. A sample size of 240 patients was determined for the two groups of this study considering the drop-out.

Efficacy analysis

The primary analysis was to compare PFS in the full analysis population using Cox proportional hazards model. The model was initially fit with the following factors: treatment, tumor site, TNM stage and PS. A backward elimination (stepwise) was applied to screen prognostic factors, and the final model would exclude all interaction terms and the terms that were not significant at a two-sided 10% level (primary site was evaluated with a single test). A 2-sided 5% significance level was applied to the estimate of the treatment hazard ratio from the final model.

Secondary efficacy analyses for the overall response rate and complete response rate between treatment groups were compared using an unadjusted X^2 test in the full analysis population. Logistic regression with backward elimination was used to explore the influence of the prognostic factors included in the PFS analysis. The response rates were compared at two time points: 1) after tumor assessment of the last cycle of chemotherapy and before locoregional radiotherapy; 2) after locoregional radiotherapy. Kaplan-Meier curves and life tables were calculated in the full analysis population for duration of response (CR+PR), and duration of complete response. Wilcoxon and logrank linear rank tests were used to compare the TTF and OS between treatment groups in the full analysis population, respectively. Both endpoints were also analyzed with a Cox proportional hazards model with backwards elimination to explore the influence of the prognostic factors in the PFS analysis.

Safety analysis

Safety analyses were performed by treatment received and included all patients who received study treatment. The safety profile of the Taxotere regimen was compared to the control group using the NCI-CTCAE V3.0 criteria.

Grade 3-4 adverse events with an overall incidence rate of 10% or more in either treatment group were identified, and the difference in the frequency of these events between the treatment groups was compared using a 2-sided Fisher's exact test. Treatment discontinuation due to an adverse event and toxic deaths was compared using Fisher's exact test.

Local Symptoms Analysis

The 3 subscales of the PSS-HN (normalcy of diet, understandability of speech, and eating in public) and the pain intensity score from the VAS were analyzed using repeated measures on the evaluable population with a baseline score and at least 1 post-randomization score. The repeated measures model included covariates for the baseline score and time of assessment relative to randomization. For analysis of the PSS-HN, the Hochberg step-up method was used to adjust the nominal significance level for the 3 comparisons for an overall 2-sided 5% significance level.

WHO performance scores were collapsed into 2 categories at each cycle: a score of 0 versus 1 to 4. Data were analyzed using generalized estimating equations (GEE) to model whether there was a treatment-group difference in the probability of a 0 score. To optimize the efficiency of the estimation, the observed correlation structure of the data was evaluated and the most appropriate and parsimonious working correlation structure was selected for the model estimation (GENMOD).

Quality of Life Analyses

The 5 primary domains for this trial were analyzed using a mixed model. The models included the baseline score, treatment group, time, and treatment by time interactions effects. The interactions were excluded when not statistically significant at a 2-sided 10% significance level. The most parsimonious covariance structure parameterization was used for the final model. The Hochberg step-up procedure was used, with an overall 2-sided 5% significance level applied to the set of 4 statistics.

Interim analysis

An interim analysis was planned when half of the patients had finished the protocol-specified study treatments (chemotherapy plus radiotherapy), aiming at learning about the short-term efficacy outcome and safety profile.

Summary:

1. Patients demographics and characteristics at baseline

A total of 239 patients were randomized from 15 centers into the study. 20 patients were excluded from the full analysis population (FAS) due to lack of source documents, and 219 patients were included in the FAS. The evaluable population (ES) was defined as all the randomized and eligible patients who must meet the following conditions: the patient must receive at least 2 cycles of treatment and have no major protocol violation related to efficacy evaluation, and each lesion at the baseline must be examined with the same imaging instrument, and 158 patients were included into the ES. 228 treated patients were included into the safety population (SS).

Table 1 presents the patients accounting of study treatment and reasons for discontinuation in the FAS. More patients discontinued chemotherapy in the PF group (33.3%) than in the TPF group (19.4%).

Table 1 Summary of completion of treatment and reasons for discontinuation (FAS)

Number (%) of patients	All (N=219)	TPF (N=108)	PF (N=111)
Patients received chemotherapy	212(96.8%)	101(93.5%)	111(100.0%)
Completed chemotherapy as per protocol	154(70.3%)	80(74.1%)	74(66.7%)
Discontinued chemotherapy	58(26.5%)	21(19.4%)	37(33.3%)
Primary reason for chemotherapy discontinuation			
Adverse event	8(3.7%)	3(2.8%)	5(4.5%)
Death	1(0.5%)	1(0.9%)	0(0.0%)
Progressive disease	9(4.1%)	2(1.9%)	7(6.3%)
Patient's request of protocol prohibited treatment	17(7.8%)	7(6.5%)	10(9.0%)
Lost to follow-up	3(1.4%)	1(0.9%)	2(1.8%)
Major protocol violation	10(4.6%)	3(2.8%)	7(6.3%)
Others	10(4.6%)	4(3.7%)	6(5.4%)
Patients received radiotherapy	153(69.9%)	76(70.4%)	77(69.4%)
Discontinuation of radiotherapy unknown	2(0.9%)	0(0.0%)	2(1.8%)
Completed radiotherapy as per protocol	123(56.2%)	62(57.4%)	61(55.0%)
Discontinued radiotherapy	28(12.8%)	14(13.0%)	14(12.6%)
Primary reason for radiotherapy discontinuation			

Toxicity	8(3.7%)	3(2.8%)	5(4.5%)
Administration route/method change	1(0.5%)	1(0.9%)	0(0.0%)
Others	19(8.7%)	10(9.3%)	9(8.1%)
Completed study treatment (chemotherapy + radiotherapy as protocol required)	109(49.8%)	57(52.8%)	52(46.8%)
Trial ongoing (Visit ongoing)	63(28.8%)	31(28.7%)	32(28.8%)
Trial ended	156(71.2%)	77(71.3%)	79(71.2%)
Reason for ending study			
Adverse event	2(0.9%)	0(0.0%)	2(1.8%)
Death	115(52.5%)	53(49.1%)	62(55.9%)
Lost to follow -up	28(12.8%)	17(15.7%)	11(9.9%)
Others	11(5.0%)	7(6.5%)	4(3.6%)

Information on chemotherapy and radiotherapy in Table 2 are summarized in the safety population, which consisted of all 228 treated patients. TPF group had longer chemotherapy duration (P=0.019) and received more average cycles (P=0.016) than PF group. The 2 treatment groups were comparable with respect to radiotherapy duration and dose.

Table 2 Delivery and duration of study treatment (SS)

	TPF (N=110)	PF (N=118)	P value
No. of patients who received chemotherapy	110	118	
Duration of chemotherapy (weeks) (mean±SD)	7.95±3.328	6.92±3.252	0.019
Median duration of chemotherapy (weeks)	8.3	6.9	
Median of relative dose intensity of chemotherapy	100%	100%	
Total no. of cycles received	345	335	
Cycles received by patient (mean±SD)	3.1±0.94	2.8±0.91	0.016
Median of cycles received by patient	3	3	
No. of cycles (%) with delay or dose reduction	89(25.8%)	75(22.4%)	
No. of patients (%) who received radiotherapy	81(73.6%)	81(68.6%)	
Duration of radiotherapy (weeks) (mean±SD)	6.92±1.437	6.80±1.407	0.578
Median duration of radiotherapy (weeks)	7.0	7.1	
Dose of radiotherapy (Gy) (mean±SD)	70.86±22.565	65.51±11.693	0.069
Median dose of radiotherapy (Gy)	70.0	70.0	
Duration of study treatment (chemotherapy + radiotherapy) (weeks) (mean±SD)	16.13±7.171	14.51±7.172	0090
Median duration of study treatment (chemotherapy + radiotherapy) (weeks)	18.1	16.1	

Demographics and baseline characteristics of the full analysis population are summarized in Table 3. The 2 treatment groups were comparable for demographics and tumor characteristics at baseline.

Table 3 Demographics and baseline characteristics (FAS)

	All (N=219)	TPF (N=108)	PF (N=111)
Age (years)			
N(missing)	219(0)	108(0)	111(0)
Median (range)	57.0 (20.0-70.0)	56.0 (23.0-70.0)	57.0 (20.0-69.0)
Sex – [n(%)]			
Male	208(95.0%)	103(95.4%)	105(94.6%)
Female	11(5.0%)	5(4.6%)	6(5.4%)
WHO PS - [n(%)]			
0	94(42.9%)	44(40.7%)	50(45.0%)
1	125(57.1%)	64(59.3%)	61(55.0%)
Primary tumor site - [n(%)]			
Oral cavity	53(24.2%)	23(21.3%)	30(27.0%)
Oropharynx	52(23.7%)	28(25.9%)	24(21.6%)
Hypopharynx and larynx	114(52.1%)	57(52.8%)	57(51.4%)
Primary tumor histological grade - [n(%)]			
Well-differentiated	44(20.1%)	22(20.4%)	22(19.8%)
Moderately differentiated	56(25.6%)	30(27.8%)	26(23.4%)
Poorly differentiated	35(16.0%)	16(14.8%)	19(17.1%)
Differentiation cannot be assessed	7(3.2%)	4(3.7%)	3(2.7%)

Unknown	77(35.2%)	36(33.3%)	41(36.9%)
Tutor staging – T - [n(%)]			
T1	5(2.3%)	3(2.8%)	2(1.8%)
T2	37(16.9%)	18(16.7%)	19(17.1%)
T3	69(31.5%)	37(34.3%)	32(28.8%)
T4	108(49.3%)	50(46.3%)	58(52.3%)
Tutor staging - N - [n(%)]			
N0	46(21.0%)	21(19.4%)	25(22.5%)
N1	35(16.0%)	17(15.7%)	18(16.2%)
N2	115(52.5%)	56(51.9%)	59(53.2%)
N3	22(10.0%)	14(13.0%)	8(7.2%)
Unknown	1(0.5%)	0(0.0%)	1(0.9%)
Tutor staging – M - [n(%)]			
M0	219(100.0%)	108(100.0%)	111(100.0%)
Total stage			
II	2(0.9%)	1(0.9%)	1(0.9%)
III	44(20.1%)	22(20.4%)	22(19.8%)
IVA	150(68.5%)	71(65.7%)	79(71.2%)
IVB	22(10.0%)	14(13.0%)	8(7.2%)
Unknown	1(0.5%)	0(0.0%)	1(0.9%)

2. Efficacy results:

2.1 Primary endpoint

At the cut-off date of 31 Jan. 2016, the median study follow-up time was 473.5 days for the TPF group and 454.0 days for the PF group.

The primary efficacy analysis was a comparison of PFS adjusted on the prognostic factors in the full analysis population using a Cox proportional hazards model. Treatment with TPF had a hazard ratio (HR) of 0.752 (95% CI: 0.532~1.062) in PFS compared to treatment with PF, when adjusted on the prognostic factors with the Cox model. The median PFS was 400.0 days in the TPF group and 342.0 days in the PF group, representing a 58.0 days increase, but no statistical significance (log-rank test, P = 0.227).

But the same analyses performed in the evaluable population showed that treatment with TPF had a HR of 0.652 (95%CI: 0.439~0.968) in PFS compared to treatment with PF, when adjusted on the prognostic factors with the Cox model. The median PFS was 462.0 days in the TPF group and 325.0 days in the PF group, demonstrating a statistically significant PFS increase (log-rank test, P = 0.041).

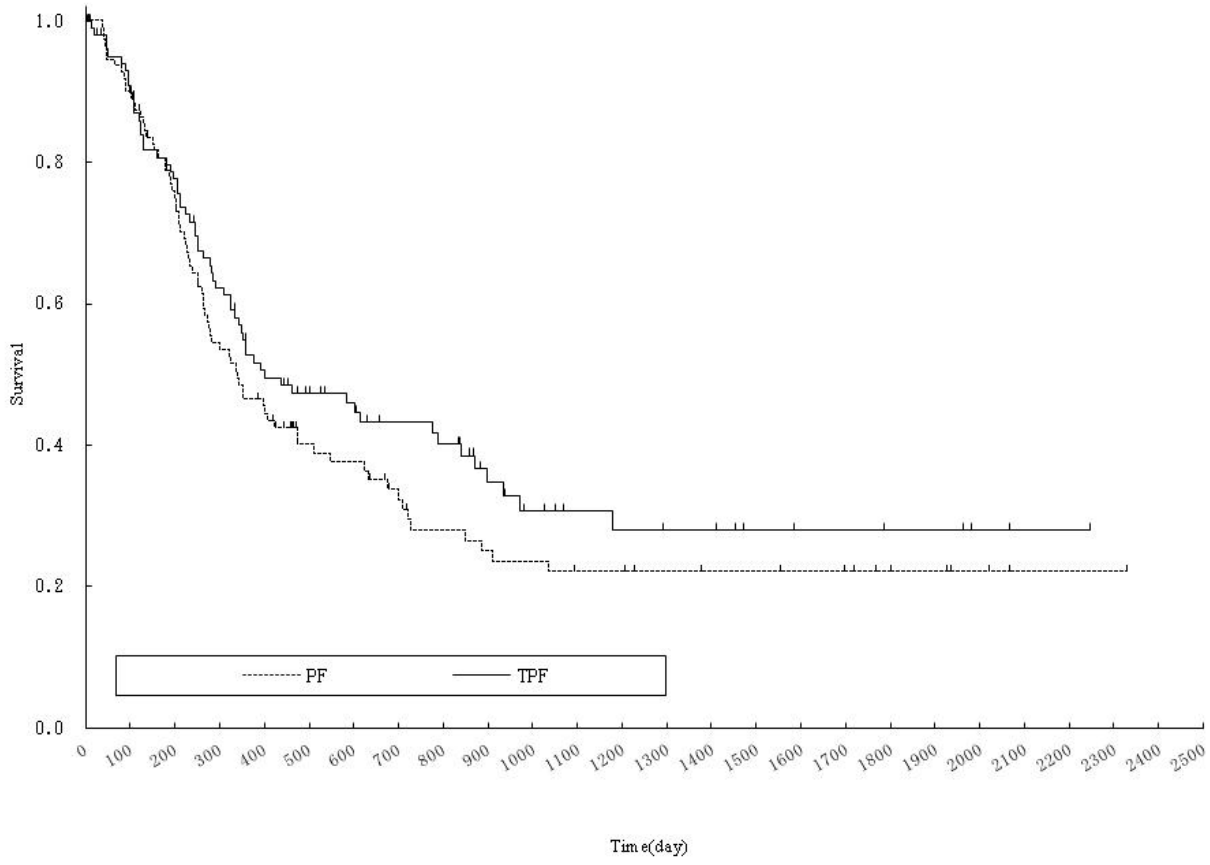

Figure 1 Progression-free survival – Kaplan-Meier curve (FAS)

2.2 Secondary endpoints

The best overall response rates after chemotherapy was statistically significant higher in the TPF group compared to the PF group (TPF: 76.3% vs. PF: 52.9%; Chi-square test, P =0.001), and the difference and 95%CI was 23.3% (10.5%~36.2%). The median duration of response in responders for chemotherapy and radiotherapy combined was 141.0 days longer in the TPF group than in the PF group without statistical significance (TPF: 734.0 days vs. PF: 593.0 days; log-rank test, P = 0.744).

Regarding time to treatment failure, a 53.0 days increase in median TTF was observed in the TPF group compared to the PF group, but with no statistical significance (TPF: 390.0 days vs. PF: 337.0 days; log rank test, P = 0.271).

The analysis of overall survival showed that a 161.0 days increase in median OS was observed in the TPF group compared to the PF group, but with no statistical significance (TPF: 787.0 days vs. PF: 626.0 days; log rank test, P = 0.469).

In summary, this study observed an increase in PFS, ORR after chemotherapy, duration of response, TTF and OS in patients with locally advanced inoperable SCCHN in Chinese population on addition of low dose of taxotere (60mg/m^2) to a combination of cisplatin and 5-FU, compared to cisplatin and 5-FU only. This study demonstrated an efficacy benefit improvement on TPF group but without statistical significance because the sample size utilized in the study was not base on statistical hypothesis.

3. Safety results:

A total of 228 patients received chemotherapy, comprising a safety population of 110 TPF-treated patients and 118 PF-treated patients.

A summary of the incidence of treat-emergent adverse events (TEAEs) in the safety population is presented in Table 4. Overall, 104(94.5%) patients in the TPF group and 110(93.2%) patients in the PF group experienced at least one TEAE, regardless of relationship to study treatment. When considering only grade 3-4 TEAEs, regardless of relationship to study treatment, a significant higher percentage of patients was recorded with at least one TEAE in the TPF group (68.2%) than in the PF group (31.4%). Most of the TEAEs were related to the study treatment.

Table 4 Summary of TEAEs (SS)

	All (N=228)		TPF (N=110)		PF (N=118)		Fisher's exact
	Event	Patient (%)	Event	Patient (%)	Event	Patient (%)	P value
All TEAEs	2239	214(93.9%)	1295	104(94.5%)	944	110(93.2%)	0.786
Treatment-related TEAEs							
Related to docetaxel	764	93(40.8%)	764	93(84.5%)	0	0(0.0%)	
Related to cisplatin	1244	185(81.1%)	745	93(84.5%)	499	92(78.0%)	0.237
Related to 5-FU	1219	182(79.8%)	734	92(83.6%)	485	90(76.3%)	0.188
Related to radiotherapy	140	65(28.5%)	77	31(28.2%)	63	34(28.8%)	1.000
Severity grade (CTC classification)							
Grade 1	1092	186(81.6%)	570	92(83.6%)	522	94(79.7%)	0.496
Grade 2	611	166(72.8%)	361	88(80.0%)	250	78(66.1%)	
Grade 3	241	101(44.3%)	168	65(59.1%)	73	36(30.5%)	
Grade 4	102	59(25.9%)	83	46(41.8%)	19	13(11.0%)	
Missing	193	61(26.8%)	113	28(25.5%)	80	33(28.0%)	
All TE-SAEs	80	47(20.6%)	68	37(33.6%)	12	10(8.5%)	<0.001
Death	10	8(3.5%)	9	7(6.4%)	1	1(0.8%)	
Require or prolongs hospitalization	56	33(14.5%)	47	25(22.7%)	9	8(6.8%)	
Congenital anomaly	0	0(0.0%)	0	0(0.0%)	0	0(0.0%)	
Life-threatening	2	2(0.9%)	1	1(0.9%)	1	1(0.8%)	
Resulted in persistent or significant disability or incapacity	0	0(0.0%)	0	0(0.0%)	0	0(0.0%)	
An important medical event	17	11(4.8%)	16	10(9.1%)	1	1(0.8%)	
Incidence≥10%, Grade 3-4 TEAEs	286	99(43.4%)	210	65(59.1%)	76	34(28.8%)	<0.001
TEAEs lead to study drug discontinuation	17	9*(3.9%)	11	4(3.6%)	6	5(4.2%)	1.000
TEAEs related to docetaxel lead to study drug discontinuation	10	3(1.3%)	10	3(2.7%)	0	0(0.0%)	0.111
TEAEs related to study drug lead to death	4	2(0.9%)	4	2(1.8%)	0	0(0.0%)	0.232

* one patient was not included in the full analysis population.
Data source: statistical report – Table 8.5.1.1

In the TPF group, the TEAEs with incidence ≥10%, regardless the relationship with study treatment, were: white blood cell count

decreased (68.2%), neutrophil count decreased (64.5%), stomatitis (52.7%), nausea (47.3%), odynophagia (36.4%), decreased appetite (30.0%), vomiting (29.1%), haemoglobin decreased (23.6%), oesophagitis (22.7%), diarrhoea (21.8%), asthenia (20.9%), rash (20.0%), weight decreased (18.2%), dry mouth (18.2%), pyrexia (15.5%), platelet count decreased (13.6%), constipation (13.6%), alanine aminotransferase increased (11.8%), hyponatraemia (10.9%) and weight increased (10.0%), and among which, grade 3-4 TEAEs with incidence ≥10% were neutrophil count decreased (45.5%), white blood cell count decreased (37.3%) and stomatitis (10.9%).

Among those events of any grade with incidence ≥10%, the events considered by investigators as docetaxel related were: white blood cell count decreased (65.5%), neutrophil count decreased (63.6%), nausea (38.2%), vomiting (24.5%), haemoglobin decreased (22.7%), decreased appetite (17.3%), diarrhoea (16.4%), asthenia (13.6%), platelet count decreased (12.7%), pyrexia (11.8%), alanine aminotransferase increased (10.9%) and hyponatraemia (10.9%), and among which, grade 3-4 docetaxel related TEAEs with incidence ≥10% were neutrophil count decreased (45.5%) and white blood cell count decreased (36.4%).

In the PF group, the TEAEs with incidence ≥10%, regardless the relationship with study treatment, were: nausea (46.6%), neutrophil count decreased (45.8%), stomatitis (44.1%), white blood cell count decreased (43.2%), decreased appetite (30.5%), haemoglobin decreased (29.7%), odynophagia (27.1%), vomiting (23.7%), rash (21.2%), dry mouth (21.2%), platelet count decreased (18.6%), oesophagitis (17.8%), asthenia (15.3%), weight decreased (12.7%), constipation (11.0%) and mucosal atrophy (10.2%), and among which, grade 3-4 TEAEs with incidence ≥10% were neutrophil count decreased (12.7%) and white blood cell count decreased (11.0%).

Table 5 Number (%) of patients with TEAEs in at least 10% of patients, by MedDRA PT (worst grade by patient) (SS)

	TPF (N=110)				PF (N=118)	
	Regardless relationship to treatment		Related to docetaxel		Regardless relationship to treatment	
MedDRA SOC/PT	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Metabolism and nutrition disorders						
Hyponatraemia	12(10.9%)	6(5.5%)	12(10.9%)	6(5.5%)	5(4.2%)	2(1.7%)
Decreased appetite	33(30.0%)	0(0.0%)	19(17.3%)	0(0.0%)	36(30.5%)	0(0.0%)
Investigations						
White blood cell count decreased	75(68.2%)	41(37.3%)	72(65.5%)	40(36.4%)	51(43.2%)	13(11.0%)
Alanine aminotransferase increased	13(11.8%)	1(0.9%)	12(10.9%)	1(0.9%)	9(7.6%)	2(1.7%)
Neutrophil count decreased	71(64.5%)	50(45.5%)	70(63.6%)	50(45.5%)	54(45.8%)	15(12.7%)
Weight decreased	20(18.2%)	5(4.5%)			15(12.7%)	1(0.8%)
Weight increased	11(10.0%)	1(0.9%)			7(5.9%)	0(0.0%)
Haemoglobin decreased	26(23.6%)	3(2.7%)	25(22.7%)	3(2.7%)	35(29.7%)	3(2.5%)
Platelet count decreased	15(13.6%)	5(4.5%)	14(12.7%)	5(4.5%)	22(18.6%)	3(2.5%)
Skin and subcutaneous tissue disorders						
Rash	22(20.0%)	3(2.7%)			25(21.2%)	4(3.4%)
General disorders and administration site conditions						
Pyrexia	17(15.5%)	2(1.8%)	13(11.8%)	2(1.8%)	9(7.6%)	0(0.0%)
Asthenia	23(20.9%)	0(0.0%)	15(13.6%)	0(0.0%)	18(15.3%)	0(0.0%)
Mucosal atrophy	9(8.2%)	0(0.0%)			12(10.2%)	1(0.8%)
Gastrointestinal disorders						
Constipation	15(13.6%)	0(0.0%)			13(11.0%)	0(0.0%)
Nausea	52(47.3%)	2(1.8%)	42(38.2%)	1(0.9%)	55(46.6%)	0(0.0%)
Diarrhoea	24(21.8%)	5(4.5%)	18(16.4%)	5(4.5%)	7(5.9%)	0(0.0%)
Dry mouth	20(18.2%)	3(2.7%)			25(21.2%)	3(2.5%)
Stomatitis	58(52.7%)	12(10.9%)			52(44.1%)	6(5.1%)
Vomiting	32(29.1%)	2(1.8%)	27(24.5%)	2(1.8%)	28(23.7%)	1(0.8%)
Oesophagitis	25(22.7%)	4(3.6%)			21(17.8%)	2(1.7%)
Odynophagia	40(36.4%)	3(2.7%)			32(27.1%)	4(3.4%)

Data source: statistical report – Table 8.5.1.8, Table 8.5.1.12 and Table 8.5.1.16

Overall, 47 of 228 (20.6%) patients experienced at least one treat-emergent SAE (TE-SAE), with 37 (33.6%) in the TPF group and

10 (8.5%) in the PF group. The TE-SAEs experienced by 2 or more patients in the TPF group were neutrophil count decreased (19 patients, 17.3%), white blood cell count decreased (4 patients, 3.6%), platelet count decreased (4 patients, 3.6%), febrile neutropenia (4 patients, 3.6%), blood bilirubin increased (2 patients, 1.8%), overdose (2 patients, 1.8%) and disease progression (2 patients, 1.8%), and in the PF group was only neutrophil count decreased (4 patients, 3.4%).

Four (3.6%) patients in the TPF group and 5 (4.2%) patients in the PF group discontinued study drug due to TEAEs. These TEAEs in the TPF group were blood bilirubin increased (2 patients), bilirubin conjugated increased, hypoalbuminaemia, cholecystitis acute, peritonitis, alanine aminotransferase increased, aspartate aminotransferase increased, pyrexia, disease progression, haemorrhagic ascites (respectively 1 patient), and in the PF group were HIV test positive, alanine aminotransferase increased, aspartate aminotransferase increased, neutrophil count decreased, mouth ulceration and deep vein thrombosis (respectively 1 patient).

Deaths due to SAE occurred in 7 (6.4%) of TPF-treated patients and in 1(0.8%) of PF-treated patient, including 2 disease progression deaths, 2 multiple-organ failure deaths, one respiratory failure death, one toxic death (white blood cell count decreased, neutrophil count decreased, platelet count decreased) and one death due to sepsis in the TPF group, and one death due to increased upper airway secretion in the PF group.

Although more TEAEs were observed in the TPF group compared with the PF group, the safety profile of TPF was consistent with the well-established safety profiles of docetaxel, cisplatin, and 5-FU in the previous studies, and no previously unknown safety issues were identified in this study. Overall, in the advanced head and neck cancer patient population, TPF has a toxicity profile that was manageable with the careful monitoring of patients and safety management practices commonly used in oncology.

4. Quality of life and clinical benefit

4.1 Quality of life

Regarding of the global health status/quality of life (GHS/QoL) from QLQ-C30, no statistically significant difference was observed between the 2 treatment groups in the full analysis population (P = 0.303), as well as for the evolution over time (P = 0.169).

The pain, swallowing, speech, and coughing scores were the 4 primary domains of the QoL analysis from QLQ-H&N35. No statistically significant treatment effect was observed for all the 4 domains (all P > 0.05) in the full analysis population. The evolution over time was statistically significant only for speech (P = 0.021). The scores of the speech decreased over time in both treatment groups during chemotherapy, but then re-increased in the follow-up period.

4.2 Clinical benefit

The PSS-H&N scale data showed that there was no statistically significant difference (all P > 0.05) between the 2 treatment groups regarding all the three subscales (normalcy of diet, understandability of speech, and eating in public).

Pain intensity were similar in both treatment groups (P=0.795). The WHO PS scores were not significantly different between the 2 treatment groups (P=0.679).

Issue date: 15-Jan-2019