



European Medicines Agency

London, 13 November 2006

Product name: **TAXOTERE**

Procedure No. **EMA/H/C/073/II/70**

SCIENTIFIC DISCUSSION

Following a change of policy the EMEA now publishes the full scientific discussion for Extension of Indication procedures (after removal of any commercially confidential information). For that reason, the information published for recent applications for a particular medicinal product may now be more detailed than what was published for applications in the past.

- Introduction

Taxotere 20 and 80 mg concentrate and solvent for solution for infusion (INN: docetaxel) were first granted a Marketing Authorisation (MA) under exceptional circumstances for a restricted indication (second line monotherapeutic treatment of patients with advanced breast cancer after anthracycline failure) in the EU in 1995. Docetaxel is, just like paclitaxel, an important taxane, which displays its cytotoxic/antineoplastic activity by promoting the assembly of free tubulin into stable microtubules.

Meanwhile, after the granting of the full MA and several amendments of the indication, the licensed therapeutic indications are:

“Breast cancer

- in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.*
- in combination with doxorubicin for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.*
- in monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy. Previous chemotherapy should have included an anthracycline or an alkylating agent.*
- in combination with trastuzumab for the treatment of patients with metastatic breast cancer whose tumors overexpress HER2 and who previously have not received chemotherapy for metastatic disease.*
- in combination with capecitabine for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.*

Non-small cell lung cancer

- in monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.*
- in combination with cisplatin for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition.*

Prostate cancer

- in combination with prednisone or prednisolone for the treatment of patients with hormone refractory metastatic prostate cancer.*

Gastric Adenocarcinoma

- in combination with cisplatin and 5-fluorouracil for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease.”*

In April 2000, the MAH submitted a type II variation (EMEA/H/C/073/II/25) to extend the indication to: *“induction treatment of patients with unresectable locally advanced squamous cell carcinoma of the head and neck (Stage III or IV) with good performance status”*.

The submission was withdrawn in July 2001, after a negative CHMP opinion. The grounds for refusal were as follows:

- The submitted documentation included only limited data from phase I/II studies with docetaxel in a small and heterogeneous patient population treated according to various regimens and modalities.
- The results provided did not establish outstanding activity of the combination regimen including docetaxel. A high variability in the 2-year overall survival (OS) results was noted in the documentation submitted so that a claim of outstanding activity for the docetaxel-containing regimen could not be established with respect to OS. The high variability observed in the submitted Phase I/II studies underlines the need for a Phase III study for a reliable evaluation of efficacy.
- The docetaxel/5FU/cisplatin regimen appeared to be relevantly more toxic than 5FU/cisplatin and this underscored the need for more convincing efficacy data.

In March 2006, the MAH submitted a new type II variation application (EMA/H/C/073/II/70), thereby amending the proposed indication into *“TAXOTERE (docetaxel) in combination with cisplatin and 5-fluorouracil is indicated for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.”*

Proposed posology:

“For the induction treatment of inoperable locally advanced squamous cell carcinoma of the head neck (SCCHN), the recommended dose of TAXOTERE is 75 mg/m² as a 1 hour infusion followed by cisplatin 75 mg/m² over 1 hour, on day one, followed by 5-fluorouracil as a continuous infusion at 750 mg/m² per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, patients should receive radiotherapy. Patients must receive premedication with antiemetics and appropriate hydration (prior to and after cisplatin administration). Prophylaxis for neutropenic infections should be administered.

For cisplatin and 5-fluorouracil dose modifications, see manufacturer’s summary of product characteristic”

This second submission is supported by a phase III study, TAX 323, comparing induction treatment with Docetaxel plus Cisplatin plus 5-Fluorouracil (TPF) to treatment with Cisplatin plus 5-Fluorouracil (PF) alone. Both arms were followed by radiotherapy treatment.

Head and neck (H&N) cancer is a group of cancers, in the same anatomical region (comprising cancers of the oral cavity, nasopharynx, pharynx and larynx) with roughly similar histology, aetiology, treatment options and prognostic variables. H&N cancers represent 5% of newly diagnosed cancers in adult patients. Worldwide, more than 500 000 new cases are projected annually. In 2002, the estimated incidence in Europe alone was around 143 000, with over 68 000 deaths. Tobacco and alcohol (abuse) are major contributors to the development of H&N cancers.

The main histological subtype within H&N cancers is squamous cell carcinoma (SCC).

The Tumour- Node- Metastasis (TNM) staging system is the best prognostic system for locally advanced squamous cell carcinoma of the H&N (SCCHN). It is an indicator of resectability, a good prognostic factor for efficacy of radiotherapy, and therefore of survival.

The survival of patients with H&N cancers depends on a number of factors, the most important being disease stage and patient performance status. Generally, patients with early-stage disease (stage I or II) can be treated effectively with surgery with or without radiotherapy (RT), or with RT alone; 5-year survival rates are in the region of 60% to 90%. Unfortunately, at the time of diagnosis, 2/3 of the patients have an advanced locoregional disease (stage III or IV), with a far worse prognosis resulting in 5-year survival rates of 60% to less than 4%. Stage III is defined as T3 N0 M0 or T1-3 N1 M0. Stage IV is defined as T4 N0-1 M0 or T1-4 N2-3 M0 or any T any N M1. Local disease is often associated with pain, mutilation, and functional/nutritional problems, which severely impair the quality of life of the patient.

SCCHN is generally considered as irresectable if all gross tumor cannot be removed on anatomic grounds or if local control cannot be achieved after an operation. For patients with a performance status (PS) of 0 or 1, the standard treatment for newly diagnosed but irresectable disease is concurrent

platinum based chemotherapy with radiotherapy (i.e. chemoradiotherapy (CRT)). However CRT is associated with a substantial increase in toxicity.

The value of adding chemotherapy to radiotherapy has been confirmed in the meta-analyse by Bourhis et al. 2004. Data showed that among 87 trials, a benefit was confined mainly to the use of concurrent CRT, which was shown to give an 8% survival advantage at 5 years. The benefit was greater when a platinum based chemotherapy was used (11% survival advantage at 5 years).

The total dose and fractionation are important factors in determining outcome of RT. "Standard-of-care" RT for subjects with locally advanced head and neck malignancies is still evolving.

Improvements in radiation technology, such as intensity-modulated radiotherapy (IMRT), offer the possibility to spare the salivary glands from the radiation effects and then to reduce acute and late toxicities, such as xerostomia. This emergent new technique does not need the administration of a radioprotectant agent. Despite the growing use of IMRT, this technique is not yet available in all radiotherapy centers. Likewise, altered fractionation radiation schedules have enabled the delivery of intensified doses of radiotherapy with improved locoregional disease control. However, this approach is generally associated with an increase in the incidence of acute grade 3/4 side effects.

The role of induction chemotherapy, i.e. neoadjuvant therapy, in the treatment of locally advanced SCCHN remains controversial despite evidence that integrating chemotherapy into the treatment plan of locally advanced disease can lead to organ preservation and improved survival of patients with resectable and irresectable disease. The results of a meta-analysis by Pignon et al (Lancet 2000) showed that neoadjuvant chemotherapy by cisplatin/5-fluorouracil (PF) prior to surgery improves the local control and has a small non-significant impact on survival in patients with SCCHN.

Phase II trials investigating induction chemotherapy with docetaxel associated to cisplatin/5-FU (TPF), have reported promising results in terms of high response rate and survival. However, these expectations needed further investigation in well-defined controlled trials.

With reference to the current variation, the pivotal randomised phase III study, XRP6976F-323/EORTC 2971 (EFC6042), compared induction chemotherapy treatment with TPF to treatment with PF in an effort to improve local control in patients with inoperable locally advanced SCCHN.

With reference to other treatment options in the field of SCCHN, photodynamic therapy with Foscan (temoporfin) received a positive opinion by the CHMP in 2001, for the palliative treatment of patients with advanced head and neck squamous cell carcinoma failing prior therapies and unsuitable for radiotherapy, surgery or systemic chemotherapy.

In August 2002, the Marketing Authorisation Application for Intradose (cisplatin/adrenaline) (Maxim Pharmaceuticals Ltd) for the treatment of recurrent or refractory squamous cell carcinoma of the head and neck in patients who are not considered candidates for surgery or radiotherapy, was withdrawn. In February 2006, the CHMP gave a positive opinion for Erbitux, molecular targeted therapy, in combination with radiation therapy for the treatment of patients with locally advanced squamous cell cancer of the head and neck.

- Clinical aspects

Clinical pharmacology

Reference is made to the pharmacokinetic interaction study, XRP6976E/1001, submitted as part of variation II-67 for the gastric adenocarcinoma indication. As study XRP6976E/1001 was assessed and discussed as part of variation II-67, it will not be commented further here.

Clinical Efficacy

Phase I/II studies

Study Tax017HN

The Tax017HN trial was a phase I/II, multicenter European study of neoadjuvant chemotherapy with Taxotere, cisplatin and 5-FU in locally advanced previously untreated HNSCC. Taxotere 75 mg/m² was administered with cisplatin 75 mg/m² (dose level I) or 100 mg/m² (dose level II) and 5-FU 750 mg/m²/day for 5 days, every 3 weeks. 48 patients were enrolled between September 1997 and September 1999, 25 in the arm receiving dose level I and 23 in the dose level II arm. All patients had stage III or IV disease without evidence of distant metastasis (M0) and had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (31.1% and 68.8%, respectively). The most prevalent tumour primary site was hypopharynx (35.4%). Treatments were administered at planned dose (90%) and without delay in a majority of cycles (92.4%). The median relative dose intensity was 0.98. Prophylactic antibiotics were administered in 43% of patients receiving dose level I and in 70% of patients receiving dose level II.

Evaluation of response was performed using CT-scan and MRI assessments reviewed by an independent expert panel. The Overall Response Rate (ORR) in the intent-to-treat population was 64% at dose Level I and 78.3% at Dose Level II. No patients had complete response. No biopsies were performed. Median survival was 18.5 months and Progression Free Survival (PFS) was 6.9 months. One-year survival in the group receiving dose level I was 56% and was not reached in dose level II. One-year-survival for the overall population was 68.7% and the 2-year-survival rate was 42%.

Dose level I (T75/P75/F750) was selected for further evaluation in the phase III trial TAX 323, since the efficacy was comparable and the safety profile better as compared to dose level II (T75/P100/F750).

Study Tax708

Tax708 was a phase I/II, multicentre US based study of neoadjuvant chemotherapy with docetaxel, cisplatin and 5-FU in curative treatment of HNSCC. In the previous application in 2000, this study was presented as the pivotal trial.

Docetaxel 75 mg/m² was administered with cisplatin 75 mg/m² (dose level I) or 100 mg/m² (dose level II) and 5-FU 1000 mg/m²/day for 4 days. 43 patients were enrolled between February 1998 and October 1999, 13 in dose level I and 30 in dose level II. 12 out of 13 patients treated at dose level I received ciprofloxacin at all 3 cycles. 23 out of 30 patients at dose level II were treated with oral ciprofloxacin prophylactically during the first cycle and 20 during the second and third cycles. The objectives of this study were to evaluate complete responses, overall response rate and pathological responses.

All patients had stage III or IV disease without evidence of distant metastasis (M0) and had ECOG performance status 0 or 1 (65.1% and 34.9%, respectively). A majority of patients (51.2%) had oropharynx tumour as primary site tumour. Treatments were administered at the planned dose (84.9%) and without delay in a majority of cycles (90.5%). The median relative dose intensity was 0.98.

In the intent-to-treat population, there were 6 patients (46.2%) with complete response (CR) (95% CI (confidence interval): 19.2% - 74.9%) among patients treated with dose level I and 11 patients (36.7%) with CRs (95% CI: 19.9% - 56.1%) among those treated at dose level II.

The overall response rate (ORR) in the intent-to-treat population was 84.6% at dose level I and 96.7% at dose level II. Median survival and progression free survival (PFS) had not yet been reached at the time of the submission. The one-year survival rate for the overall population was 97% and the 2-year survival rate (cut-off date of 15 August 2000) was 82%.

Because the efficacy and safety profiles of dose level II (T75/P100/F1000) were considered better than those of dose level I, dose level II was selected for evaluation in the randomized comparative phase III trial TAX 324.

Phase III study - TAX323

Methods

First patient was randomised on 14 April 1999; clinical cut-off date for progression-free survival (PFS) was 21 September 2003. The study was conducted by the Sponsor (Aventis Pharma, now part of the Sanofi-Aventis Group) in cooperation with the European Organization for Research and Treatment of Cancer (EORTC).

Objectives

Primary

To compare the progression-free survival (PFS) in 2 groups of subjects with locally advanced inoperable Squamous Cell Carcinoma of head and neck (SCCHN):

- docetaxel plus cisplatin plus 5-FU (TPF- test group) followed by locoregional radiation therapy.
- cisplatin plus 5-FU (PF – control group) followed by locoregional radiation therapy.

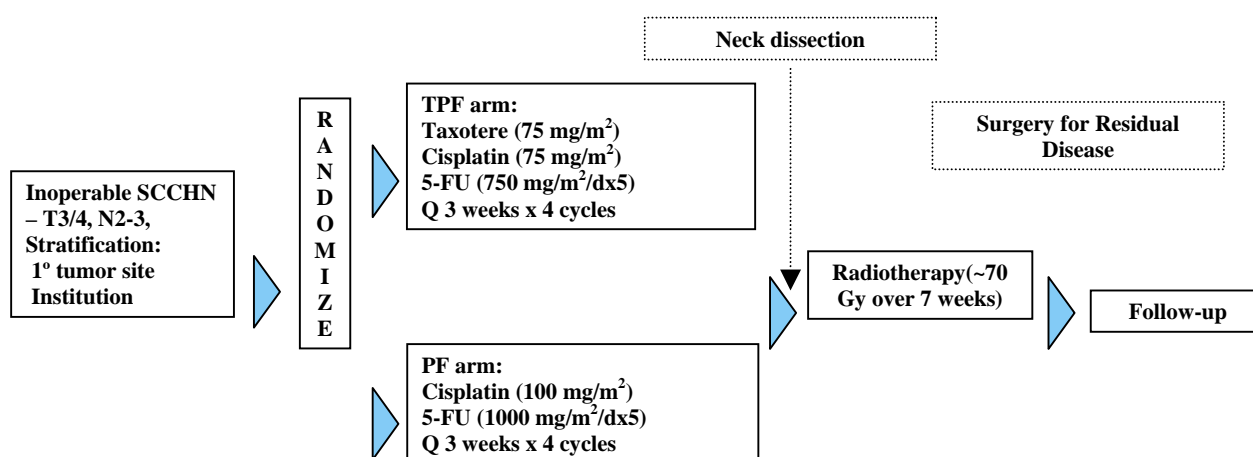
Secondary

To evaluate and compare response rates before and after radiation therapy, local symptoms, duration of response, time to treatment failure, survival, toxicity and the quality of life (QOL) between the test group and the control group.

Study Design

TAX323 is a multicenter, non-blinded, randomized, stratified, phase III study comparing 2 combination therapy regimens as induction treatment before radiotherapy for locally advanced, inoperable SCCHN. Patients were randomized to receive either the triple test therapy (TPF) or control treatment (PF) followed by locoregional radiotherapy in both groups.

Randomization was stratified upon 2 factors: the primary tumor site (oral cavity versus oropharynx versus hypopharynx versus larynx) and the center (i.e. institution).



Tumor assessment with computerized axial tomography scan / magnetic resonance imaging / (CAT scan/MRI) of the head and neck was performed at the following times during the study:

- Pre-study;
- After Cycle 2 of chemotherapy (Day 21);
- After completion of chemotherapy (days 21 to 28 of Cycle 4);

- 12 weeks after completion of radiotherapy;
- On follow-up visits; and
- At any time if suspicion of disease progression.

Protocol amendments

Three protocol amendments were performed:

- Amendment 1 - August 1999: Modification/clarification of the study design and conduct of the study which did not affect the Statistical Analysis Plan (SAP).
- Amendment 2 - October 2000: Specification of criteria for inoperability and cancellation of the external review of response.
- Amendment 3 - April 2001: Modification of criteria for inoperability and conduct of the study not affecting the SAP.

Study Participants

The main inclusion criteria were:

- Inoperable squamous cell carcinoma of the head and neck (excluding nasopharynx, nasal and paranasal cavities);
- Uni- or bidimensionally measurable disease;
- Stage III or IV, M0 (without metastases) ;
- No previous chemotherapy, radiotherapy, or surgery;
- Age 18 to 70;
- WHO performance status of 0 or 1;
- Adequate renal, liver, and hematological function.

Treatment regimen

Chemotherapy:

Test group (TPF): Taxotere 75 mg/m², as a one-hour intravenous (i.v.) infusion, followed by cisplatin 75 mg/m², administered as a one-hour i.v. infusion on Day 1. 5-FU was administered after cisplatin as a continuous i.v. infusion at 750 mg/m² per day for 5 days.

Control group (PF): Cisplatin 100 mg/m², administered as a one-hour i.v. infusion on Day 1, followed by continuous i.v. infusion of 5-FU 1000 mg/m² per day for 5 days.

Patients were to receive 4 cycles of chemotherapy at 3-week intervals unless progression of disease (PD) or unacceptable toxicity occurred, or the patient refused treatment.

Radiotherapy:

In the absence of progressive disease, patients in both treatment arms should receive 7 weeks of radiation therapy following chemotherapy (irrespective of whether they completed or discontinued chemotherapy) with a minimum interval of 4 weeks and no later than 7 weeks after start of the last cycle (day 28 to day 49 of last cycle).

The irradiated volumes include the primary site and both sides of the neck. Radiation should be delivered using either a conventional fractionation (1.8 Gy - 2.0 Gy, 1x/day, five days per week - total dose of 66 to 70 Gy), or accelerated/hyperfractionated regimens of radiation therapy (2 times a day, with a minimum inter-fraction interval of 6 hours, five days per week, scheme at the discretion of the center - up to a total of maximum 70 Gy for accelerated regimens and of maximum 74 Gy for hyperfractionated schemes). Each institution will commit itself to treat all subjects with one of these regimens (conventional or hyperfractionated) prior to study start.

Chemotherapy followed by radiation therapy are both integral part of the study treatment.

Surgery:

Neck dissection between chemotherapy and radiotherapy and surgery for residual disease after radiotherapy were performed at the discretion of the local multidisciplinary team.

Subjects with progressive disease were treated according to the standard of care of each participating center and were followed for survival.

Premedication:

· *TPF arm:* dexamethasone 8 mg bid (D1 to 3) and ciprofloxacin 500 mg bid (D5 to 15).

· *Both arms:* antiemetics; G-CSF secondary prophylaxis allowed.

All patients were to be followed in the study until documentation of death.

Comparator:

Study TAX323 used Cisplatin (100 mg/m²) plus 5-fluorouracil (1000 mg/m²) as control arm.

Endpoints

Primary: Progression-free survival (PFS).

Secondary: Overall survival (OS), Overall response rate (ORR), Duration of response, Time to treatment failure (TTF).

PFS - was calculated from the date of randomization until the date of progression or death (regardless of the reason for death), whichever occurred first. If progression or death did not occur before the cut-off date (or occurred after the cut-off date), the patient was censored at the last valid assessment date before the cut-off date (at the cut-off date otherwise).

OS - was measured from the date of randomization until death (regardless of the reason for death). If death or last contact did not occur before the cut-off date, the patient was censored at the cut-off date, or the last contact date if the patient was lost to follow-up before the cut-off date.

RR - is defined for each treatment group as the percentage of patients in the group who achieve a complete response (CR) or a partial response (PR) according to WHO criteria. Responses calculated by the study coordinator at the end of the induction chemotherapy and after the administration of radiation therapy were used in the analyses.

The duration of overall response (PR + CR) was calculated from the date of randomization up to the documentation of progression in the responders for the whole treatment (induction chemotherapy plus radiotherapy). If progression or death did not occur before the cut-off date/further anti-cancer therapy date (or occurred after the cut-off date), the patient was censored at the last valid assessment date before the cut-off date/further anti-cancer therapy date (at the cut-off date otherwise).

TTF - was calculated from the date of randomization up to the date of failure (progression, relapse, death, discontinuation of study treatment [chemotherapy or radiotherapy] due to AE, patient refusal of chemotherapy treatment, or lost to follow-up before the end of treatment [chemotherapy plus radiotherapy]). If none of these events occurred before the cut-off date or occurred after the cut-off date, the patient was censored at the date of last valid assessment before cut-off date; at the cut-off date otherwise. Patients lost to follow-up after the end of the treatment (as defined above) were censored at the date of last contact if it occurred before the cut-off date; at the cut-off date otherwise. Patients not treated were censored at their randomization date.

Quality of life evaluation:

Two EORTC quality of life instruments were used in this study. The global quality of life domain of the QLQ-C30 questionnaire and pain, swallowing, speech, and coughing from the QLQ-H&N35 module were used. Evaluations were made before randomisation, after two cycles, at the end of chemotherapy before starting radiotherapy, at six and nine months post end of radiotherapy.

Clinical benefit:

The *performance status scale for head and neck* (PSS-HN) developed and validated by M. List was used to evaluate the disabilities of subjects. It measures disturbances of speech and eating. Assessments were those used for quality of life evaluation.

Pain - (past 24 hours) was measured using a 100 mm scale. Assessments were those used for quality of life evaluation.

WHO performance status score - was recorded at baseline, on day 1 of each cycle before treatment, at the end of chemotherapy, at the end of radiotherapy and in every follow-up after end-of-therapy.

Sample size

The primary endpoint, PFS, was analysed in the Intent-to-treat population. To demonstrate that the experimental treatment increased the median PFS by 50%, i.e. 10 versus 15 months in the PF and TPF treatment groups, respectively, with a 2-sided 5% significance level and a 85% power, and a 5% lost to follow-up rate, 348 patients were to be recruited (174 in each treatment group) in order to observe 260 events. It was anticipated that the accrual time would last 24 months followed by a further follow-up of 12 months.

A 2-stage design was initially planned to minimize the number of patients treated with the test regimen under the null hypothesis (H₀), as the test regimen was anticipated to be more toxic. The stage 1 analysis was planned to be performed half-way through the total accrual period when 42 events would have been observed. Due to trial execution issued the interim analysis (i.e., stage 1) was cancelled. Only the final analysis (stage 2) was performed.

Statistical methods

Four study populations were defined: an intent-to-treat (ITT) population, a safety population (SP), a radiotherapy safety population (RSP), and an evaluable for response population.

Tests used

A 2-sided 5% significance level was applied to all tests.

Time-to-event data were described using Kaplan-Meier curves and compared with the log-rank and Wilcoxon linear rank tests and in Cox's proportional hazards model.

For multivariate analyses, five baseline variables were fitted to the model for each analysis: treatment, tumour site (oral cavity primary, oropharynx primary, hypopharynx primary versus larynx primary), T stage, N stage, and WHO performance status (WHO-PS).

Chi-square tests or Fisher's exact tests were used to compare groups on categorical variables.

Logistic or proportional odds models were used to adjust for prognostic factors.

A mixed model including the baseline score, treatment group, time, and treatment by time interactions effects were used to analyse quality of life data.

Primary efficacy analysis

The primary efficacy analysis at the end of the study was a comparison of PFS in the intent-to-treat (ITT) population using a Cox's proportional hazard model. In addition, Kaplan-Meier curves and life tables were calculated in the ITT population.

Secondary efficacy analyses

Secondary efficacy analyses were carried on OS, ORR, TTF.

Several sensitivity analyses were planned on the primary and secondary endpoints.

Interim analysis

Although planned no interim analysis was performed due to delays in data collection, data monitoring and validation. By the time the interim analysis was feasible, 90% of the planned patients were already recruited and safety data on the tested TPF treatment was available from phase II study and ongoing phase III studies.

Follow up

All patients were to be followed in the study until documentation of death.

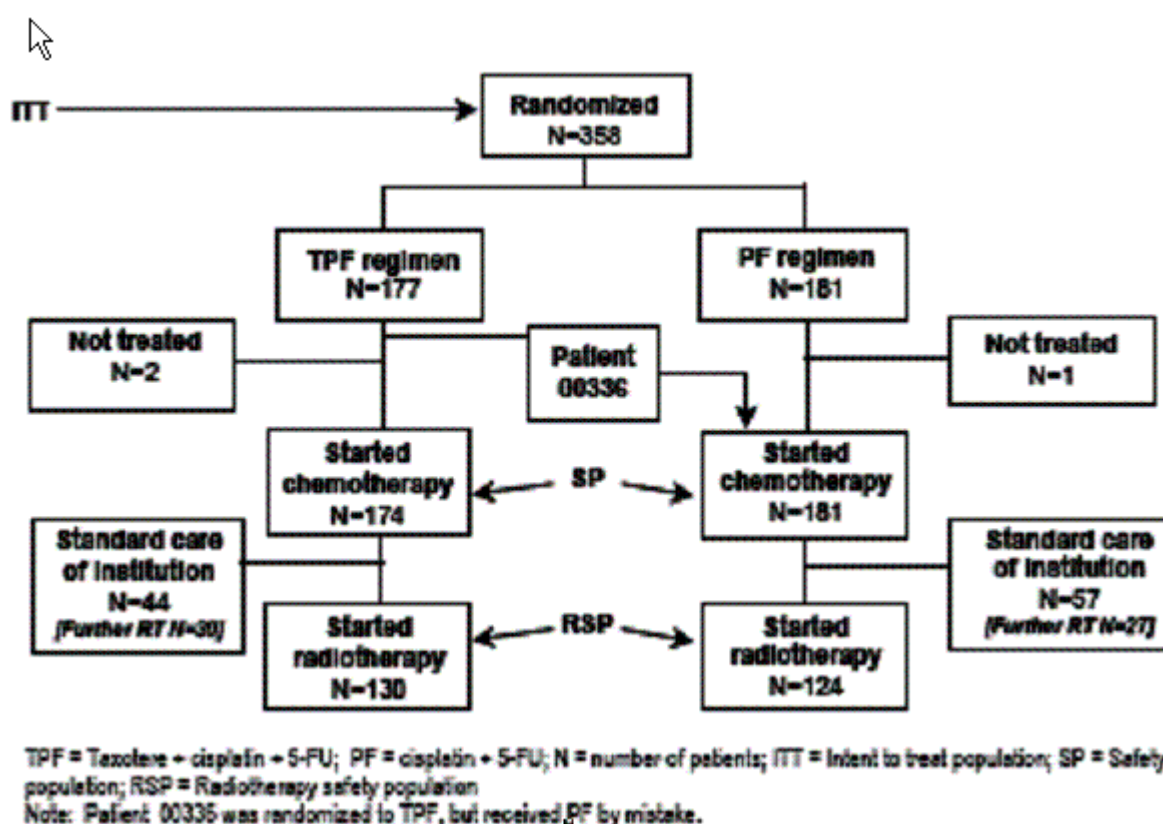
Efficacy results

There were 358 patients randomized over 35 months. Thirty-seven centers in 15 countries randomized patients in this study. As defined in the SAP, the cut-off date was chosen to include at least 260 PFS events. The occurrence of the 260th event was reported to the EORTC data center on 21 September 2003, which corresponds to an overall median follow-up of 33.7 months.

Disposition of patients

Patient disposition over the course of the study is presented in Figure 1

Figure 1 – Summary flowchart of patient disposition



Baseline data

Demographic and tumor characteristics at baseline are shown in Table 1 below.

Table 1 – Demographics and tumor characteristics at baseline in TAX 323 (ITT)

	RANDOMIZATION GROUP		
	TPF (N = 177)	PF (N = 181)	ALL (N = 358)
Sex			
Male	159 (89.8%)	162 (89.5%)	321 (89.7%)
Female	18 (10.2%)	19 (10.5%)	37 (10.3%)
Age (years)			
Median (min-max)	53 (30-69)	52 (30-70)	53 (30-70)
< 65	156 (88%)	163 (90.0%)	319 (89%)
≥ 65	18 (10.2%)	18 (9.9%)	36 (10.1%)
WHO PS			
0	90 (50.8%)	91 (50.3%)	181 (50.6%)
1	86 (48.6%)	90 (49.7%)	176 (49.2%)
2	1 (0.6%)	0 (0.0%)	1 (0.3%)
Anatomic site			
Hypopharynx	53 (29.9%)	52 (28.7%)	105 (29.3%)
Larynx	12 (6.8%)	13 (7.2%)	25 (7.0%)
Oral cavity	31 (17.5%)	32 (17.7%)	63 (17.6%)
Oropharynx	81 (45.8%)	84 (46.4%)	165 (46.1%)
Histopathological grade			
Well differentiated	28 (15.8%)	32 (17.7%)	60 (16.8%)
Moderately differentiated	83 (46.9%)	90 (49.7%)	173 (48.3%)
Poorly differentiated	39 (22.0%)	31 (17.1%)	70 (19.6%)
Undifferentiated	1 (0.6%)	0 (0.0%)	1 (0.3%)
Differentiation cannot be assessed	3 (1.7%)	3 (1.7%)	6 (1.7%)
Missing	23 (13.0%)	25 (13.8%)	48 (13.4%)
Clinical T			
T1	3 (1.7%)	1 (0.6%)	4 (1.1%)
T2	11 (6.2%)	16 (8.8%)	27 (7.5%)
T3	40 (22.6%)	34 (18.8%)	74 (20.7%)
T4	123 (69.5%)	130 (71.8%)	253 (70.7%)

	RANDOMIZATION GROUP		
	TPF (N = 177)	PF (N = 181)	ALL (N = 358)
Clinical N			
N0	16 (9.0%)	26 (14.4%)	42 (11.7%)
N1	28 (15.8%)	29 (16.0%)	57 (15.9%)
N2	101 (57.1%)	104 (57.5%)	205 (57.3%)
N3	31 (17.5%)	20 (11.0%)	51 (14.2%)
NX	1 (0.6%)	2 (1.1%)	3 (0.8%)
Number of organs involved			
1	18 (10.2%)	23 (12.7%)	41 (11.5%)
2	153 (86.4%)	143 (79.0%)	296 (82.7%)
3 or more	5 (2.8%)	12 (6.6%)	17 (4.7%)
Unknown	1 (0.6%)	3 (1.7%)	4 (1.1%)
Main organs involved ^a			
Lymph nodes	157 (88.7%)	155 (85.6%)	312 (87.2%)
Hypopharynx	110 (62.1%)	110 (60.8%)	220 (61.5%)
Mouth	27 (15.3%)	29 (16.0%)	56 (15.6%)
Tongue	20 (11.3%)	23 (12.7%)	43 (12.0%)
Larynx	12 (6.8%)	16 (8.8%)	28 (7.8%)
Tonsil	10 (5.6%)	6 (3.3%)	16 (4.5%)

T = Docetaxel; P = Cisplatin; 5-FU = 5-Fluorouracil; WHO PS = World Health Organization Performance Status; T = primary tumor; N = nodal involvement; M = metastasis;

^a Organ involved in at least 5% of patients in at least one treatment group. A patient may have had several organs involved.

Primary efficacy endpoint

The *primary efficacy analysis* was the comparison of the PFS in the ITT population based on a Cox proportional hazards model. The results of the Cox model adjusted for the potential effect of the prognostic factors on PFS are shown in Table 2 below.

Table 2 - Cox proportional hazards model (full model) intent to treat population - progression-free survival (ITT)

Covariate	Adjusted treatment effect on prospectively selected covariates			
	P value	Hazard ratio	95% CI	
			Lower	Upper
Randomization group: TPF / PF	0.0042	0.70	0.55	0.89
WHO performance score: PS null/ PS \geq 1	0.0322	0.77	0.61	0.98
N stage: N2-3/N0-N1-NX	0.0360	1.34	1.02	1.77
Hypopharynx primary: yes/no ^a	0.0616	1.01	0.60	1.72
Oropharynx primary: yes/no ^a	.	0.77	0.46	1.29
Oral cavity primary: yes/no ^a	.	1.17	0.67	2.06
T stage: T4/T2-T3-T1	0.7495	1.05	0.78	1.41

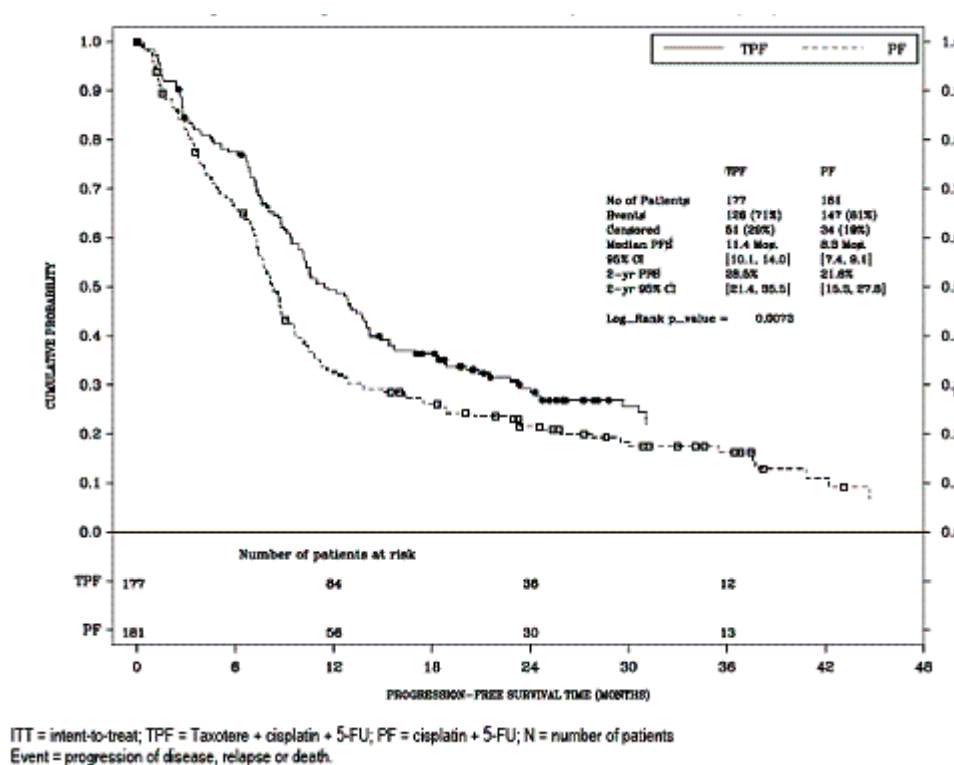
ITT = intent-to-treat; CI = confidence interval; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; WHO = World Health Organization; PS = performance status

^a The reference for each primary site variable is the larynx primary site. Then, these variables were evaluated with a single test.

Kaplan-Meier analysis

Median time to progression was higher in the TPF treatment group (11.4 months, 95% CI: 10.1-14.0) than in the PF treatment group (8.3 months, 95% CI: 7.4-9.1), representing a 3.1-month increase. The difference between the 2 treatment groups was statistically significant (log-rank test, $P = 0.0073$) with a 28% progression risk reduction for the TPF treatment group compared to the PF treatment group (HR 0.72, 95% CI: 0.57-0.92).

Figure 2 – Progression-free survival – Kaplan-Meier curve (ITT)



- Sensitivity analysis on PFS

The results on the primary endpoint were similar whether non-tumor related deaths or further therapies were used as the censoring event.

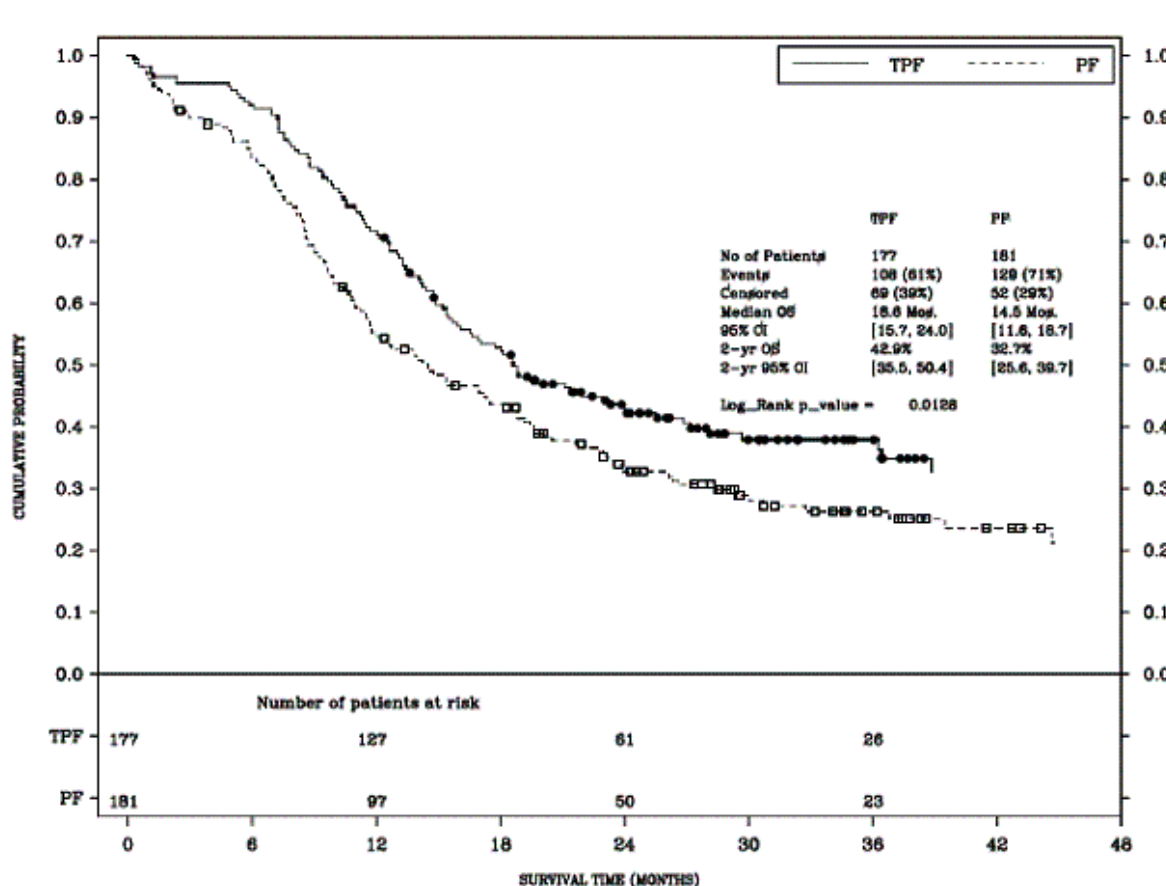
Secondary efficacy endpoints

Overall Survival

At the cut off date, 237 of 358 (66.2%) patients had died (61.0% and 71.3% in the TPF and PF treatment groups, respectively). The proportion of patients lost to follow-up was similar in the 2 treatment groups (3.9% overall).

Figure 3 presents a Kaplan-Meier plot for OS

Figure 3 – Overall survival – Kaplan-Meier curve (ITT)



Median time to death was longer in the *TPF* treatment group (18.6 months, 95% CI: 15.7-24.0) than in the *PF* treatment group (14.5 months, 95% CI: 11.6-18.7). The difference between the treatment groups was statistically significant (HR 0.72, 95% CI: 0.56-0.93; log-rank test, $P = 0.0128$). A 3-years survival rate estimate of 37.9% for TPF versus 26.3 for PF, was reported.

Response

Best overall response to chemotherapy in the ITT population is summarized in Table 3 below.

Table 3 - Best overall response to chemotherapy (ITT)

	Randomization group	
	TPF (N=177)	PF (N=181)
Complete response	15 (8.5%)	12 (6.6%)
Partial response	105(59.3%)	85 (47%)
No change	30 (16.9%)	45 (24.9%)
Progression of disease	10 (5.6%)	12 (6.6%)
Not evaluable	17 (9.6%)	27 (14.9%)
Overall RR (CR+PR) 95% CI	67.8% [60.4-74.6]	53.6% [46.0-61.0]
P value	0.006	
Complete RR (CR) 95% CI	8.5% [4.8-13.6]	6.6% [3.5-11.3]
P value	0.509	

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; RR = response rate; CR = complete response; PR = partial response; CI = confidence interval

Best overall response (BOR) taking into account both chemotherapy and radiotherapy periods is summarized for the ITT population in Table 4 below.

Table 4 - Best overall response to chemotherapy and radiotherapy (ITT)

	Randomization group	
	TPF (N=177)	PF (N=181)
Complete response	59 (33.3%)	36 (19.9%)
Partial response	69 (39%)	70 (38.7%)
No change	24 (13.6%)	39 (21.5%)
Progression of disease	11 (6.2%)	13 (7.2%)
Not evaluable	14 (7.9%)	23 (12.7%)
Overall RR (CR+PR) 95% CI	72.3% [65.1-78.8]	58.6% [51.0-65.8]
P value	0.006	
Complete RR (CR) 95% CI	33.3% [26.4-40.8]	19.9% [14.3-26.5]
P value	0.004	

ITT = intent-to-treat; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; RR = response rate; CR = complete response; PR = partial response; CI = confidence interval; BOR= best overall response

In order to explore the impact of surgery before PD on best overall response rate, Table 5 presents the best overall response in the primary (ITT) population and patients without surgery before PD. The response rates were in the same range for both populations; the 95% CI for these populations overlap.

Table 5 - Best overall response in the ITT population (primary) and in patients without surgery before PD - by period

BOR(CR+PR)	POPULATION	TPF		PF	
		RR	95% CI	RR	95% CI
CT	Primary	120/177 (67.8%)	[60.4-74.6]	97/181 (53.6%)	[46.0-61.0]
	Without surgery before PD	106/160 (66.3%)	[58.4-73.5]	91/171 (53.2%)	[45.4-60.9]
RT	Primary	76/130 (58.5%)	[49.5-67.0]	54/124 (43.5%)	[34.7-52.7]
	Without surgery before PD	63/113 (55.8%)	[46.1-65.1]	53/116 (45.7%)	[36.4-55.2]
CT & RT	Primary	128/177 (72.3%)	[65.1-78.8]	106/181 (58.6%)	[51.0-65.8]
	Without surgery before PD	113/160 (70.6%)	[62.9-77.6]	100/171 (58.5%)	[50.7-66.0]

CT=chemotherapy; RT=radiotherapy; BOR= best overall response

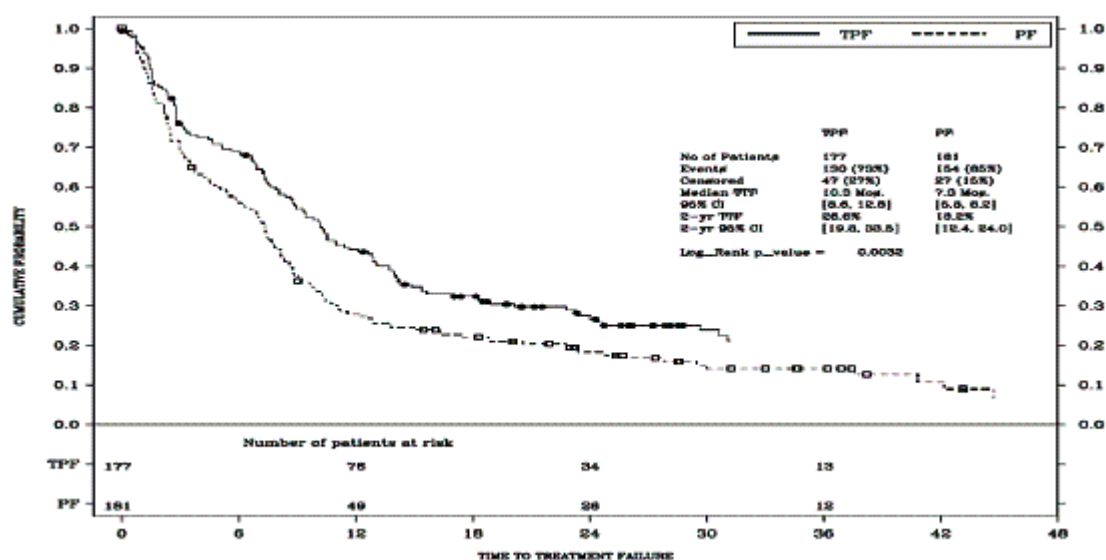
Duration of response

Median duration of response was higher in the *TPF* treatment group (15.7 months; 95% CI: 13.4-24.6) than in the *PF* treatment group (11.7 months; 95% CI: 10.2-17.4). This difference was statistically significant (HR 0.72, 95% CI: 0.52-0.99; log-rank test, $P = 0.0457$).

Time to treatment failure

Kaplan-Meier plots are presented in Figure 4 below:

Figure 4 – Time to treatment failure Kaplan-Meier curve (ITT)



Analysis of efficacy by subgroup - gender, age, and race

Subgroup analyses were performed to assess the effects of gender and age on measures of efficacy; data on race were not recorded in this study. Females comprised 10.2% of the TPF treatment group and 10.5% of the PF treatment group, and patients aged 65 and above comprised 10.2% of the TPF treatment group and 9.9% of the PF treatment group.

Quality of life

The self-administered EORTC questionnaires (QLQ-C30 and QLQ-H&N35) were used and completed at 5 different time points (at baseline, at the end of Cycle 2, Cycle 4, and then 6 months and 9 months after end of study treatment).

As expected, the compliance decreased over time. At the end of chemotherapy treatment, the compliance was 72.7% in the TPF treatment group versus 67.7% in the PF treatment group. Nine months after completion of study treatment, it decreased to 40.7% in the TPF treatment group versus 47.8% in the PF treatment group.

The global health status/quality of life (GHS/QoL) score was one among the primary endpoints of the QoL analysis. For the EORTC QLQ-C30 GHS/QoL, the treatment effect was significantly ($P = 0.01$) lower in favour of TPF. The deterioration of the global health score during study was statistically lower for the TPF treatment group compared to the PF treatment group.

Using the QLQ-H&N35 data, the mean score of the four endpoints increased over time in both treatment arms, corresponding to a worsening of patient condition. However, because of the low compliance (about 30% of patients were compliant), no conclusion can be drawn concerning the effect of treatment.

Clinical Benefit

At baseline, almost all patients completed the *PSS-HN assessment*. The percentages decreased with time to approximately 50 to 55% at the end of treatment and over. Both groups reported deterioration during follow up. The deterioration was statistically greater for patients in the PF arm. Using a mixed model approach, a statistically significant ($P = 0.0064$) difference for normalcy of diet score was observed between the two treatment arms favouring TPF; similar results were observed for understandability of speech ($P < 0.0001$) and for eating in public ($P = 0.0002$). *Pain intensity* increased significantly with time ($P < 0.001$). No treatment effect was noticed.

WHO performance status score was evaluated in more than 90% of patients. The WHP PS score was not significantly different between the two treatment arms: HR = 0.963 (95% CI, 0.66 to 1.41). Using Kaplan-Meier estimate, median time to first deterioration was higher in the TPF treatment group (13.7 months; 95% CI, 10.7 to 21.0) than in the PF treatment group (8.3 months; 95% CI, 7.3 to 9.6). The difference between the two treatment arms was statistically significant (log-rank test, $P = 0.0158$) with a 30% deterioration of WHO PS risk reduction for TPF compared to PF (HR = 0.70; 95% CI, 0.52 to 0.94).

Discussion on Clinical Efficacy

Phase I/II – Tax017HN and Tax708

The phase I/II studies Tax017HN and Tax708 were part of the previous submission in 2000. No updated data are provided as part of this resubmission. Several criticisms were raised by the CHMP in 2001, particularly with reference to the design and the conduct of the studies. Compared to TAX708, Tax017HN included a larger proportion of patients with hypopharynx as primary site of the tumour, which was associated with worse prognosis than oropharynx. The tumour burden of patients was

higher in TAX017HN compared to TAX708 (48% of patients with T4 tumours in TAX017HN compared to 21% in TAX708. 29% of patients had N3 disease in TAX017HN compared to 14% of patients in TAX708.

Results from the study TAX017HN did not confirm the high response rates observed in study TAX708. Furthermore, the treatment regimen used in study TAX017HN is different from that used in study TAX708. Otherwise, in the neoadjuvant setting of SCCHN, outcome of therapy depends not only on induction chemotherapy but also on loco-regional treatment (radiotherapy and/or surgery) following induction chemotherapy. However, outcome after complete treatment in study TAX708 has not been provided.

Thus, differences in drug schedules and patient populations may explain the differences in results observed. Consequently, the heterogeneous results rendered the analysis particularly difficult. The data could only be considered as indicative of an activity of TPF in this medical setting, but not sufficient to support an extension of indication of Taxotere. In 2001, the CHMP preferred to postpone the final assessment until the results of the randomised Phase III trials were available for a reliable evaluation of the benefit/risk ratio.

For this second submission, study TAX017HN could be considered as the basis for dose schedule selection for study TAX323.

Phase III Study – TAX323

Treatment of advanced SCCHN is complex and involves not only chemotherapy but also radiotherapy and surgery. The role of induction chemotherapy, i.e., neoadjuvant therapy, in the treatment of locally advanced SCCHN remains controversial despite evidence that integrating chemotherapy into the treatment plan of locally advanced disease can lead to organ preservation and improved survival of patients with resectable and unresectable disease.

The results of a meta-analysis of chemotherapy of SCCHN by Pignon et al. 2000, showed that neoadjuvant chemotherapy by cisplatin/5-fluorouracil (PF) prior to surgery improves the local control and has a small non-significant impact on survival. At the time of study initiation, reference chemotherapy treatment in this neoadjuvant setting of SCCHN was cisplatin 100 mg/m² plus 5-fluorouracil 1000 mg/m² (Paccagnella A et al. 1994). Therefore the control arm is acceptable.

At the time when the TAX323 study was designed, concomitant CT-RT was not an accepted standard option. However, neo-adjuvant CT was also not a validated option (and is still not). So, from a scientific point of view, the study design should have been TPF+ RT vs RT alone. One can assume that survival after PF+RT is not lower than after RT alone. However, the chosen study design with docetaxel as an add-on to neoadjuvant PF-chemotherapy allows an assessment of the impact of docetaxel in this multimodal approach. The higher rate of early deaths in the PF arm in study TAX323 remains unexplained.

Thus, the current standard treatment of locally advanced SCCHN would be chemotherapy concurrently administered with radiotherapy (chemoradiotherapy).

The MAH has made a commitment to submit the final clinical study report of the US study TAX324 (induction therapy followed by chemoradiation in patients with inoperable or low surgical SCCHN investigation) as soon as it is available for CHMP review.

Endpoints -TAX 323

According to the Guideline on the evaluation of anticancer medicinal products in man (CHMP/EWP/205/95/Rev. 3) acceptable primary endpoints for phase III therapeutic confirmatory studies should be time related. Overall survival is considered the most appropriate endpoint. However, for the tumor entity SCCHN the combination of primary endpoint PFS with the key secondary endpoint overall survival is considered acceptable to assess the clinical benefit of TPF.

The study was conducted in collaboration with a recognised institution, EORTC, and an Independent Data Monitoring Committee (IDMC) was established.

The originally planned external review of responses was cancelled, as PFS was the primary endpoint of the study (Protocol Amendment 2). It is well recognised in this population that review of radiologic images alone is not sufficient for adequate tumor assessment because of many confounding factors such as inflammation, oedema, and large necrotic lymph nodes. The response assessment of locally advanced SCCHN is mostly clinical and in an open trial, a blinded assessment would be preferable. In order to provide unbiased results, the independent “blinded” review of images could have been changed into an Independent Clinical Review Committee (ICRC).

In SCCHN, local disease is often associated with pain, mutilation, and functional/nutritional problems, which severely impair the quality of life of the patient. Therefore the assessment of QOL and local clinical benefit is appropriate. The QOL questionnaire and the specific H&N PS scale used were appropriate.

Chemotherapy

As discussed above, study TAX323 used Cisplatin (100 mg/m²) plus 5-fluorouracil (1000 mg/m²) as control arm. At the time of study initiation, reference chemotherapy treatment in this neoadjuvant setting of SCCHN was cisplatin 100 mg/m² plus 5-fluorouracil 1000 mg/m² (Paccagnella A et al. 1994). Therefore the control arm is acceptable.

A majority of patients in both treatment groups completed chemotherapy as per protocol: 70.1% in the TPF treatment group and 61.9% in the PF treatment group. Completion of chemotherapy as per protocol” includes patients who completed chemotherapy either after 2 cycles or after 4 cycles”.

In the TPF treatment group, 137 patients (78.7%) received 4 cycles of chemotherapy and in the PF treatment group 119 (65.7%) patients received 4 cycles.

Chemotherapy was discontinued in 52 (29.4%) of the patients in the TPF treatment group and in 68 (37.6%) patients in the PF treatment group. In both treatment groups, the most frequent reasons for discontinuation from study medication were progressive disease (TPF: 24 patients, 13.6%; PF: 20 patients, 11.0%), AEs (TPF: 11 patients, 6.2%; PF: 21 patients, 11.6%) and death (TPF: 6 patients, 3.4%; PF: 12 patients, 6.6%).

The potential impact in the number of toxic deaths within 30 days of last chemotherapy (4 in the TPF arm, 10 in the PF arm) on PFS was explored in an exploratory analysis censoring for these events. Based on the corresponding hazard ratio and its 95% confidence interval (i.e. 0.74 [0.58-0.95]) one can exclude an impact of higher toxic death rate in the control arm on PFS outcomes.

The potential impact in the number of toxic deaths within 30 days of last chemotherapy (4 in the TPF arm, 11 in the PF arm) on OS was explored in an exploratory analysis censoring for these events. Although the analysis is consistent (HR=0.75, 95% CI: 0.58-0.97) with the primary overall survival analysis (HR=0.72, 95% CI: 0.56-0.93) a lower HR was reported when toxic deaths are censored. Despite the fact that, the benefit of TPF compared to PF on the survival curves appeared early (within 2 to 6 months) after the start of chemotherapy, one can exclude an impact of higher toxic death rate within 30 days of last chemotherapy in the control arm on OS outcomes.

It should also be taken into account that in study TAX323, the duration of a planned complete treatment is 6 months: 12 weeks for chemotherapy followed 4 to 7 weeks later by radiotherapy for up to 7 weeks.

Dose reductions were made in 7.5% of patients in the TPF arm and in 12.7% of patients in the PF arm. The most frequent reason for dose reduction in both treatment groups was drug related toxicities (TPF: 4.6%; PF: 11.0%). Taxotere dose modifications were indicated when patients experienced neutropenia and/or its complications, cutaneous reactions (grade 3 or 4, but not nail changes), elevated bilirubin, or impaired liver function.

The median relative dose intensity was greater than 0.90 in both study arms.

Upon request, the Applicant performed an analysis on the patient group that completed chemotherapy as intended. Both subgroup OS and PFS analyses are consistent with primary analyses favouring the TPF arm. The benefit of TPF seems not to be linked to a suboptimal dosing of PF.

Radiotherapy

Radiotherapy was planned for all patients who were not in progression at their last cycle of chemotherapy. The majority of patients who started chemotherapy received radiotherapy as per protocol in both treatment groups: 74.7% of TPF treated patients (130 patients), and 68.5% of PF-treated patients (124 patients). However, 47 patients in the TPF treatment group (26.6%), and 57 patients in the PF treatment group (31.5%) did not receive radiotherapy as per protocol, but standard care according to institution practice. Unfortunately, the CRF did not document reasons why protocol radiotherapy was not delivered.

Most patients in both treatment groups received conventional radiotherapy (TPF: 77.7%; PF: 77.2%). The median total dose of radiotherapy delivered was 70 Gy in 7 weeks in median in both treatment groups.

Surgery

Surgery was performed at the discretion of the local multidisciplinary team.

More patients in the TPF arm had surgery during the study: 45 patients (25.9%) in the TPF treatment group and 27 patients (14.9%) in the PF. For 17 patients in the TPF treatment group and 9 patients in the PF treatment group, surgery was performed before PD occurred.

An exploratory analysis was performed to evaluate whether surgery performed before progression influenced PFS. The hazard ratio and its 95% confidence interval were 0.76 [0.60-0.97] (with censoring on first surgery before progression). The benefit remained in favour of the tested arm.

Baseline data

Demographic and tumor characteristics at baseline were well balanced: most patients were men (89.7%); the median age was 53 years, with a range of 30 to 70 years. All patients except 1 in the TPF treatment group had WHO performance status of 0 or 1.

The most frequent tumor site was the oropharynx (46.1% of patients). The most frequent clinical TNM stage in both treatment groups was T4 / N2. In 83% of patients, 2 organs were involved, the most common being lymph nodes and hypopharynx.

The population of patients with SCCHN is heterogeneous and exclusion of patients with particular history of disease (such as nasopharynx, nasal and paranasal cavities) is adequate. Co-morbidities are often associated with SCCHN and patients often present a low performance status. In this study, patients should have had a good performance status (WHO PS 0 or 1). Otherwise the results of the primary efficacy analysis on PFS, Cox model adjusted for the potential effect of the prognostic factors confirmed the prognostic value of PS ($p=0.032$).

Prophylactic treatment

According to the protocol a majority of patients in each arm received prophylactic treatment with antiemetics and corticosteroids. Secondary Prophylactic G-CSF was used in a minority of patients (less than 10% in each arm).

The less frequent prophylactic antibiotic treatment administered in the control arm (6.6% vs 94.3% in TPF) might have had an impact on patient outcome. Indeed, as discussed above, more toxic deaths (within 30 days of last chemotherapy) were reported in the PF arm (10 patients) versus in the TPF arm (4 patients). Higher doses of PF in the control than in the tested arm (PF100/100 vs TPF 75/75/750), a two times higher rate of Grade 4 neutropenia in the TPF arm (49% vs 24%) could have biased the survival analysis. Although, exploratory analyses on PFS and survival did not evidence any impact on results when toxic deaths within 30 days of last chemotherapy were censored.

Further treatment

Chemotherapy was the most common further anti-cancer therapy during follow-up: 25 patients (19.2%) in TPF arm versus 29 patients (23.4%) in PF arm. The type of chemotherapy was not specified in the study report.

Results

The primary efficacy analysis reached statistical significance in favour of TPF with a 30% progression risk reduction compared to treatment with PF, when adjusting for the prognostic factors (WHO PS, primary tumor site: HR= 0.70 (95% CI: 0.55-0.89; P = 0.0042). Although the PFS assumptions considered during sample size calculation were not reached, statistical significance has been reached in favour of TPF: Median PFS was higher in the TPF treatment group (11.4 months, 95% CI: 10.1-14.0) than in the PF treatment group (8.3 months, 95% CI: 7.4-9.1), (HR 0.72, 95% CI: 0.57-0.92; log-rank test, P = 0.0073).

As requested unadjusted analyses for PFS and OS only including the stratification factors tumour localisation and center (addressed as geographical region) in the Cox model were presented. The results are consistent with the overall primary analyses results presented. Additional sensitivity analyses including tumour localisation and center size in the model were performed. The treatment effect is similar in small and large centers and is in accordance with the overall primary PFS and OS analyses.

About 80% of patients reported a locoregional relapse and about 9% reported a distant relapse. The analyses of PFS by type of relapse report a Hazard Ratio similar to the overall PFS analysis i.e. still in favor of TPF arm (HR for Overall PFS: 0.72; HR for locoregional PFS: 0.74; HR for distant PFS: 0.73).

The absolute numbers of relapses are lower for TPF in all subgroups (locoregional, distant and undefined relapse). A higher proportion of relapses (recurrent/local or metastasis) was reported in the TPF tested arm. This could be explained by the higher rate of “undefined” relapses in the PF control arm (10.3% vs 5%).

Secondary analyses supported the conclusions of the primary ones:

- median overall survival (TPF: 18.6 months; PF: 14.5 months) showed a 28% risk reduction of death as compared to the PF treatment group and a 3-years survival rate estimate of 37.9% for TPF (versus 26.3 for PF).
- Best overall response to study treatment (chemotherapy + radiotherapy) (TPF: 72.3%; PF: 58.6%),
- duration of response (TPF: 15.7 months; PF: 11.7 months), and
- time to treatment failure (TPF: 10.3 months; PF: 7.3 months) were all in favour of TPF as compared to PF.

All of these differences were statistically significant. Although the claimed indication is based on a single pivotal open trial, the difference in OS survival at three years is about 10% absolute and this is considered clinically relevant.

The CHMP consider that clinical efficacy of docetaxel associated with treatment with cisplatin /5-FU has been demonstrated with reference to PFS, OS, and ORR. Overall efficacy data are considered sufficiently robust to support regulatory approval of TPF in the induction treatment of inoperable SCCHN.

The results of QOL and clinical benefit were consistently in favour of TPF supporting the benefit of TPF excepted, pain intensity, which was comparable between both arms.

In conclusion, statistically significant efficacy results as measured by the primary endpoint (PFS) and the secondary endpoint (OS) are associated with improved QoL and longer preservation of PS.

Clinical Safety

Docetaxel plus cisplatin and 5-FU (TPF) was administered to patients with SCCHN in 3 sponsored clinical trials: Two phase I-II studies, TAX 708 and TAX 017, and the pivotal phase III study, TAX 323. A total of 449 patients were enrolled in these studies, and of these, 446 were evaluable for safety. The studies are described below in Table-6.

Table 6 – Overview of studies

Study	Title	No. of included/ treated patients	Dosage/combination	Max No of cycles
TAX 017	Docetaxel in combination with cisplatin and 5-fluorouracil in patients with advanced, previously untreated squamous cell carcinoma of the head and neck: phase I-II study	48/48	<u>Docetaxel</u> : 75 mg/m ² , i.v., D1 every 3 weeks <u>Cisplatin</u> : 75 mg/m ² , i.v. (dose level I) or 100 mg/m ² , i.v. (dose level II), D1; every 3 weeks <u>5-FU</u> : 750 mg/m ² /D, c.i. D1 to D5; every 3 weeks	4
TAX 708	A Phase I-II Pilot Study of Induction Chemotherapy with Docetaxel in combination with Cisplatin and 5-Fluorouracil (5-FU) in Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN)	43/43	<u>Docetaxel</u> : 75 mg/m ² , i.v., D1 every 3 weeks <u>Cisplatin</u> : 75 mg/m ² , i.v. (dose level I) or 100 mg/m ² , i.v. (dose level II), D1; every 3 weeks <u>5-FU</u> : 1000 mg/m ² /D, c.i. D1 to D4 every 3 weeks	3
TAX 323	A Randomized Phase III Multicenter Trial 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	358/355	Test group (TPF) <u>Docetaxel</u> : 75 mg/m ² , i.v., D1 every 3 weeks <u>Cisplatin</u> : 75 mg/m ² , i.v., D1; every 3 weeks <u>5-FU</u> : 750 mg/m ² /D, c.i. D1 to D5; every 3 weeks Control group (PF) <u>Cisplatin</u> : 100 mg/m ² , i.v., every 3 weeks <u>5-FU</u> : 1000 mg/m ² , c.i., D1 to D5 every 3 weeks	4

Studies TAX 708 and TAX 017

The tolerability profile of TPF (Toxic death and Grade 3-4 Adverse Events) is summarized in the following table, compared to the platinum-5FU regimen of the 3 reference PF studies:

	TPF - TAX 708	TPF - TAX017HN
Toxic death	0%	4.2%
Leukopenia	65%	54%
Stomatitis	30%	17%
Nausea/Vomiting	26%	13%
Anemia	7%	25%
Renal toxicity	0%	0%
Cardiotoxicity	0%	0%

Despite the use of prophylactic antimicrobial treatment in 81% of patients, the incidence of febrile neutropenia was 18.6% and neutropenic infection was 8%. The rates of febrile neutropenia and neutropenic infection in study TAX017HN were 5% and 4%, respectively.

A majority of deaths were due to infectious complications despite co-medications administered.

Pivotal study – TAX323

Patient exposure

The total safety population (SP) includes 355 patients: 174 in the TPF treatment group, and 181 in the PF treatment group. The safety population for the radiotherapy period (RSP) includes only patients who received locoregional radiotherapy in absence of disease progression.

The total radiotherapy safety population includes 254 patients: 130 in the TPF treatment group, and 124 in the PF treatment group.

Chemotherapy:

As measured by relative dose intensity, median number of cycles administered, and mean duration of treatment, extent of exposure to chemotherapy was similar in the 2 treatment groups.

Table 7 - Overview of exposure to chemotherapy (SP)

	TPF (N=174)	PF (N=181)
Relative dose intensity	97%	91%
Median no. of cycles administered	4	4
Median duration	12.00	12.14
Patients who received 4 cycles	78.7%	65.2%

SP = safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients

Radiotherapy:

The dose and duration of locoregional radiotherapy was comparable between the 2 treatment groups.

Table 8 - Total dose of radiotherapy received (RSP)

	Treatment received	
	TPF (N=130)	PF (N=124)
Total dose of PTVI+PTVII (Gy)		
Number	129 ^a	124
Median	70.00	70.00
Mean	68.532	69.160
SEM	0.5860	0.8833
Minimum	28.00	14.40
Maximum	87.60	112.00
Total duration of PTVI+PTVII (weeks)		
Number	130	124
Median	7.14	7.14
Mean	7.041	7.001
SEM	0.1511	0.1143
Minimum	0.00	2.14
Maximum	18.14	10.00

RSP = radiotherapy safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients; SEM = Standard error of the mean

^a Patient 00135 (TPF) had a missing dose in PTVII.

All Treatment-emergent Adverse events (TEAE)

Overview of TEAEs during chemotherapy:

96.6% of patients receiving chemotherapy experienced at least 1 TEAE. The percentages of patients who experienced at least 1 possible/probable related TEAE or 1 TEAE regardless of relationship, were higher in the TPF treatment group than in the PF treatment group [(TPF: 96.6%; PF: 87.8%) and (TPF: 99.4%; PF: 93.9%), respectively].

Grade 4 events were reported in 9.2% of patients in the TPF treatment group and 11.6% in the PF treatment group.

Drug-related grade 4 events were reported in 5.2% of patients in the TPF treatment group and 8.3% in the PF treatment group.

Table 9 - Overview of number of patients with TEAEs during chemotherapy (SP)

	Treatment received	
	TPF (N=174)	PF (N=181)
Number of patients on chemotherapy		
With at least one TEAE	173 (99.4%)	170 (93.9%)
With at least one grade 3/4 TEAE	68 (39.1%)	70 (38.7%)
With at least one grade 4 TEAE	16 (9.2%)	21 (11.6%)
With at least one TEAE related	168 (96.6%)	159 (87.8%)
With at least one grade 3/4 TEAE related	55 (31.6%)	50 (27.6%)
With at least one grade 4 TEAE related	9 (5.2%)	15 (8.3%)

TEAE = treatment-emergent adverse event; SP = safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU;
N = number of patients

Overview of TEAEs during radiotherapy:

95,7% of patients receiving radiotherapy experienced at least 1 TEAE. The percentages of patients who experienced at least 1 TEAE, both regardless of relationship to radiotherapy and possibly or probably related to radiotherapy, were similar in the 2 treatment groups

Table 10 - Overview of patients with TEAEs during radiotherapy (RSP)

	Treatment received	
	TPF (N=130)	PF (N=124)
Number of patients on radiotherapy		
- With at least one TEAE	124 (95.4%)	119 (96.0%)
- With at least one grade 3/4 TEAE	66 (50.8%)	62 (50.0%)
- With at least one grade 4 TEAE	19 (14.6%)	19 (15.3%)
- With at least one TEAE related	113 (86.9%)	112 (90.3%)
- With at least one grade 3/4 TEAE related	56 (43.1%)	53 (42.7%)
- With at least one grade 4 TEAE related	15 (11.5%)	17 (13.7%)

TEAE = treatment-emergent adverse event; RSP = radiotherapy safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients

TEAEs by NCIC CTG Category and Term

During chemotherapy treatment:

Reported TEAEs were similar in the 2 treatment groups for most NCIC CTG categories. Only the skin category presented a >10% difference in any grade TEAE between the 2 treatment groups (TPF: 84.5%; PF: 55.2%).

Skin and gastrointestinal organ systems presented grade 3/4 TEAEs with a frequency of >10% between treatment groups [(TPF: 12.1%; PF: 1.7%) and (TPF: 10.9%; PF: 23.2%) respectively].

The neurologic organ system had grade 3/4 TEAEs with a frequency of >3% between the treatment groups (TPF: 2.9%; PF: 6.6%).

The 5 most frequent NCIC CTG terms for TEAEs were alopecia (TPF: 81.0%; PF: 43.1%), nausea (TPF: 47.1%; PF: 51.4%), stomatitis (TPF: 42.5%; PF: 47.0%), lethargy (TPF: 40.8%; PF: 38.1%), and vomiting (TPF: 26.4%; PF: 38.7%).

Grade 3-4 TEAE, with a difference in frequency of >3%, were noted for nausea (TPF: 0.6%; PF: 7.2%); stomatitis (TPF: 4.0%; PF: 11.0%); vomiting (TPF: 0.6%; PF: 5.0%); and alopecia (TPF: 10.9%; PF: 0%).

Table 11 - Patients with TEAEs during chemotherapy, by NCIC CTG category, regardless of relationship to study medication (SP)

NCIC CTG classification	Treatment received			
	TPF		PF	
	(N=174)		(N=181)	
Number of patients without TEAE	1 (0.6%)		11 (6.1%)	
Number of patients with TEAE	173 (99.4%)		170 (93.9%)	
	Grade 3/4	All	Grade 3/4	All
Skin	21 (12.1%)	147 (84.5%)	3 (1.7%)	100 (55.2%)
Gastrointestinal	19 (10.9%)	140 (80.5%)	42 (23.2%)	147 (81.2%)
Flu-like symptoms	9 (5.2%)	100 (57.5%)	6 (3.3%)	103 (56.9%)
Weight ^a	1 (0.6%)	76 (43.7%)	1 (0.6%)	84 (46.4%)
Neurologic	5 (2.9%)	73 (42.0%)	12 (6.6%)	75 (41.4%)
Infection	18 (10.3%)	48 (27.6%)	14 (7.7%)	47 (26.0%)
Cardiovascular	12 (6.9%)	42 (24.1%)	14 (7.7%)	44 (24.3%)
Pulmonary	6 (3.4%)	42 (24.1%)	9 (5.0%)	38 (21.0%)
Cancer related symptoms	9 (5.2%)	37 (21.3%)	9 (5.0%)	35 (19.3%)
Hypersensitivity		11 (6.3%)		5 (2.8%)
Ocular		8 (4.6%)		3 (1.7%)
Genitourinary	1 (0.6%)	5 (2.9%)	1 (0.6%)	4 (2.2%)
Other	1 (0.6%)	5 (2.9%)	5 (2.8%)	12 (6.6%)
Hepatic	2 (1.1%)	4 (2.3%)		
Coagulation	1 (0.6%)	1 (0.6%)		
Endocrine		1 (0.6%)		
Osseous		1 (0.6%)		
Blood bone marrow			1 (0.6%)	2 (1.1%)
Dentition				3 (1.7%)

TEAE = treatment-emergent adverse event; SP = safety population; NCIC CTG = National Cancer Institute of Canada Clinical Trials Group; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients

^a The NCIC CTG category includes weight gain and weight loss.

Notes:

Percentages have been calculated on the total number of patients.

For the number of patients with TEAEs and for each NCIC CTG classification, patients having one or more NCIC CTG term are counted only once.

For each patient, only the maximum grade recorded for the same NCIC CTG term is taken into account into the calculations.

During radiotherapy:

Reported TEAEs occurring during radiotherapy were also similar for most NCIC CTG categories of events. Only the pulmonary category presented a >10% incidence difference in any grade TEAE between the 2 treatment groups (TPF: 15.4%; PF: 26.6%).

Gastrointestinal and skin organ systems presented grade 3/4 TEAEs with a frequency of >10% between treatment groups [(TPF: 45.4%; PF: 44.4%) and (TPF: 17.7%; PF: 17.7%) respectively]. Of note, the ongoing events for patients who still had TEAEs at the start of radiotherapy belonged primarily to these 2 categories.

Flu-like symptoms and pulmonary organ system had grade 3/4 TEAEs with >3% difference between the 2 treatment groups: [(TPF: 0.0%; PF: 3.2%) and (TPF: 0.0%; PF: 3.2%) respectively]

The 5 most frequent TEAEs were stomatitis (TPF: 85.4%; PF: 87.1%), esophagitis/dysphagia/odynophagia (TPF: 61.5%; PF: 61.3%), rash/itch (TPF: 38.5%; PF: 41.1%), weight loss (TPF: 25.4%; PF: 31.5%), and skin disorder (TPF: 19.2%; PF: 21.0%).

Grade 3-4 TEAEs, with a difference in frequency of >3%, were noted for stomatitis (TPF: 38.5%; PF: 33.9%); rash/itch (TPF: 6.2%; PF: 9.7%); lethargy (TPF: 0.0%; PF: 3.2%); and shortness of breath (TPF: 0.0%; PF: 3.2%).

Related adverse events

During chemotherapy:

The 2 treatment groups were similar for most NCIC CTG categories related to treatment.

Skin and gastrointestinal categories had Grade 3-4 TEAEs with a frequency of >10% in either treatment group [(TPF: 12.1%; PF: 1.1%) and (TPF: 8.6%; PF: 20.4%) respectively].

Neurologic category had grade 3/4 TEAEs with >3% difference between the 2 treatment (TPF: 0.6%; PF: 4.4%).

The ocular disorders that developed in the TPF treatment group were consistent with the known safety profile of Taxotere (1.7% tearing disorders/ 1.1% conjunctivitis). The grade 3/4 hepatic disorder appears to be a liver failure in a patient with pre-existing liver cirrhosis (patient 00256).

The 2 treatment groups were similar for most NCIC CTG terms related to treatment. The 5 most frequent related TEAEs were alopecia (TPF: 79.9%; PF: 42.5%), nausea (TPF: 43.7%; PF: 49.2%), stomatitis (TPF: 42.0%; PF: 45.9%), lethargy (TPF: 37.9%; PF: 29.8%) and vomiting (TPF: 25.9%; PF: 35.9%).

Grade 3/4 related TEAE with >3% difference in incidence between the 2 treatment groups were as follows : stomatitis (TPF: 4.0%; PF: 11.0%), nausea (TPF: 0.6%; PF: 6.6%) and vomiting (TPF: 0.6%; PF: 4.4%) and alopecia (TPF: 10.9%; PF: 0%) which was more frequent in the TPF treatment group.

The following related TEAEs occurring in <5% of patients were considered to be clinically meaningful considering the known safety profiles of docetaxel, cisplatin, or 5-FU : dysrhythmias (TPF: 0.6%; PF: 1.1%), myocardial ischemia (TPF: 1.7%; PF: 0.6%), gastrointestinal bleeding (TPF: 1.1%), tearing (TPF: 1.7%), and conjunctivitis (TPF: 1.1%; PF: 0.6%). Of these, grade 3-4 related TEAEs were seen for dysrhythmias (TPF: 0.6%), myocardial ischemia (TPF: 1.7%), and gastrointestinal bleeding (TPF: 0.6%).

During radiotherapy:

The 2 treatment groups were similar for most NCIC CTG categories of events related to treatment during radiotherapy. No category had a >10% difference in incidence of any grade related TEAE between the 2 treatment groups.

Gastrointestinal and skin categories had a >10% frequency of grade 3/4 related TEAE [(TPF: 38.5%; PF: 37.1%) and (TPF: 15.4%; PF: 16.1%)].

No category had a difference >3% in grade 3/4 related TEAEs between the 2 treatment groups.

The incidence of infection, any grade, was higher in the patients previously treated in the PF treatment group (TPF: 5.4%; PF: 13.7%).

The 2 treatment groups were similar for most NCIC CTG terms related to radiotherapy.

The 5 most frequent TEAEs were stomatitis (TPF: 76.9%; PF: 75.8%), esophagitis/dysphagia/odynophagia (TPF: 51.5%; PF: 54.0%), rash/itch (TPF: 33.8%; PF: 33.9%),

weight loss (TPF: 20.8%; PF: 21.8%), and other: skin disorder (TPF: 17.7%; PF: 20.2%). Grade 3/4 stomatitis occurred in >10% of patients within both treatment groups (TPF: 33.1%; PF: 28.2%) as for esophagitis/dysphagia/odynophagia (TPF: 19.2%; PF: 21.8%). Radiotherapy-related infections had approximately an 8% higher incidence in the PF treated patients that received radiotherapy (PF: 13.7%; TPF: 5.4%).

TEAEs during treatment

The following related TEAEs occurring in <5% of patients were considered to be clinically meaningful considering the known safety profiles of Taxotere, cisplatin, or 5-FU: dysrhythmias (TPF: 0.6%; PF: 1.7%), myocardial ischemia (TPF: 1.7%; PF: 0.6%); gastrointestinal bleeding (TPF: 1.1%; PF: 0.0%); tearing (TPF: 1.7%; PF: 0.0%); and conjunctivitis (TPF: 1.1%; PF: 0.6%). Of these, grade 3-4 TEAEs (related) were seen for dysrhythmias (TPF: 0.6%, PF: 0.6%); myocardial ischemia (TPF: 1.7%; PF: 0.0%); and gastrointestinal bleeding (TPF: 0.6%; PF: 0.0%).

Adverse events during the follow-up (reported as late radiation toxicities 90 days after the end of study)

Patients were reevaluated 12 weeks after the completion of the radiotherapy treatment period to assess the radiotherapy late effects. The frequency by patient of RTOG AEs was 73.8% in the TPF treatment group and 65.3% in the PF treatment group, with most of the difference due to the RTOG criterion salivary glands (TPF: 63.1%; PF: 50.0%) and mucus membranes (TPF: 43.1%; PF: 31.5%), reflecting the RT field. Frequencies of RTOG AEs were generally similar for the 2 treatment groups.

Serious adverse events

Serious TEAEs during chemotherapy:

27.6% patients in the TPF treatment group and 34.8% in the PF treatment group, experienced at least 1 serious TEAE.

Among patients with serious TEAE, 21.8% in the TPF arm and 27.6% in the PF arm experienced TEAE related to study treatment.

Table 12 - Overview of number of patients with serious TEAEs during chemotherapy (SP)

	Treatment received	
	TPF (N=174)	PF (N=181)
Number of patients under chemotherapy		
With at least one serious TEAE	48 (27.6%)	63 (34.8%)
With at least one serious grade 3/4 TEAE	37 (21.3%)	46 (25.4%)
With at least one serious grade 4 TEAE	21 (12.1%)	25 (13.8%)
With at least one serious TEAE related	38 (21.8%)	50 (27.6%)
With at least one serious grade 3/4 TEAE related	30 (17.2%)	35 (19.3%)
With at least one serious grade 4 TEAE related	15 (8.6%)	21 (11.6%)

TEAE = treatment-emergent adverse event; SP = safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients

The 2 treatment groups were similar for most NCIC CTG terms for serious TEAEs (TPF: 27.6%; PF: 34.8%) as for serious related TEAEs (TPF: 21.8% ; PF: 27.6%).

The most frequent ($\geq 5\%$ in either group) related SAE terms were: infection (TPF: 6.9%; PF: 6.1%), fever in absence of infection (TPF: 5.7%; PF: 2.8%), hemoglobin (TPF: 2.9%; PF: 5.0%), and stomatitis (TPF: 1.7%; PF: 5.0%).

Table 13 - Patients with study drug-related serious TEAEs during chemotherapy, by NCIC CTG term, of all grades, in at least 2 patients (SP)

NCIC CTG term	Treatment received	
	TPF (N=174)	PF (N=181)
Number of patients without serious TEAE	136 (78.2%)	131 (72.4%)
Number of patients with serious TEAE	38 (21.8%)	50 (27.6%)
Infection	12 (6.9%)	11 (6.1%)
Fever in absence of infection	10 (5.7%)	5 (2.8%)
White blood count ^a	8 (4.6%)	8 (4.4%)
Hemoglobin ^b	5 (2.9%)	9 (5.0%)
Diarrhea	3 (1.7%)	5 (2.8%)
Gastrointestinal pain/cramping	3 (1.7%)	1 (0.6%)
Ischemia myocardial	3 (1.7%)	1 (0.6%)
Lethargy	3 (1.7%)	3 (1.7%)
Platelets ^c	3 (1.7%)	4 (2.2%)
Stomatitis	3 (1.7%)	9 (5.0%)
Creatinine	2 (1.1%)	4 (2.2%)
Febrile neutropenia	2 (1.1%)	1 (0.6%)
Granulocytes ^d	2 (1.1%)	5 (2.8%)
Hypokalemia	2 (1.1%)	2 (1.1%)
Cardiac function	1 (0.6%)	3 (1.7%)
Other: dehydration	1 (0.6%)	3 (1.7%)
Altered hearing		3 (1.7%)
Anorexia		3 (1.7%)
Nausea		4 (2.2%)
Vomiting		5 (2.8%)

TEAE = treatment-emergent adverse event; SP = safety population; NCIC CTG = National Cancer Institute of Canada Clinical Trials Group; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients

^a leucopenia, ^b anemia, ^c thrombocytopenia, ^d neutropenia

Notes:

Percentages have been calculated on the total number of patients.

For the number of patients with TEAEs and for each NCIC CTG classification, patients having one or more NCIC CTG term are counted only once.

For each patient, only the maximum grade recorded for the same NCIC CTG term is taken into account into the calculations.

Serious TEAEs during radiotherapy:

A total of 37 patients (14.6%) who received radiotherapy per protocol experienced at least 1 serious TEAE regardless of relationship to radiotherapy.

As expected for head and neck cancer radiotherapy, SAEs were mainly due to mucosal disorders. There was a difference of $\geq 3\%$ in the incidence by patient between the treatment groups in stomatitis

(TPF: 3.8%; PF: 7.3%) and esophagitis/dysphagia/odynophagia (TPF: 3.1%; PF: 6.5%). Overall, results are comparable between the 2 treatment groups.

Table 14 - Patients with serious TEAEs during radiotherapy, by NCIC CTG term, of all grades regardless of relationship in at least 2 patients (RSP)

NCIC CTG term	Treatment received	
	TPF (N=130)	PF (N=124)
Number of patients without serious TEAE	113 (86.9%)	104 (83.9%)
Number of patients with serious TEAE	17 (13.1%)	20 (16.1%)
Stomatitis	5 (3.8%)	9 (7.3%)
Esophagitis/dysphagia/odynophagia	4 (3.1%)	8 (6.5%)
Infection	3 (2.3%)	5 (4.0%)
Venous	2 (1.5%)	1 (0.8%)
Lethargy	1 (0.8%)	2 (1.6%)
Fever in absence of infection		2 (1.6%)
Shortness of breath		2 (1.6%)

TEAE = treatment-emergent adverse event; RSP = radiotherapy safety population; NCIC CTG = National Cancer Institute of Canada Clinical Trials Group; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients

Notes:

Percentages have been calculated on the total number of patients.

For the number of patients with TEAEs and for each NCIC CTG classification, patients having one or more NCIC CTG term are counted only once.

For each patient, only the maximum grade recorded for the same NCIC CTG term is taken into account into the calculations.

Deaths on study

A total of 253 (71.3%) treated patients died during the study: 115 (66.1%) in the TPF arm and 138 (76.2%) in the PF arm. There were 8 deaths (8/174 = 4.6%) in the TPF treatment group and 22 deaths (22/181 = 12.2%) in the PF treatment group within 30 days of last administration of study treatment. In both treatment groups, one-half of the deaths occurring within 30 days of last study medication were due to toxicity, and, in both treatment groups, most toxic deaths on chemotherapy occurred within the first 2 cycles. The majority of deaths occurring more than 30 days after last study treatment were due to progression of disease.

Table 15 - Summary of deaths (SP)

	Treatment received	
	TPF (N=174)	PF (N=181)
Total deaths ^a	115 (66.1%)	138 (76.2%)
Within 60 days of first administration of study treatment ^b	6 (3.4%)	12 (6.6%)
Progression of disease	0 (0.0%)	2 (1.1%)
Toxicity	3 (1.7%)	6 (3.3%)
Infection not due to protocol treatment	2 (1.1%)	0 (0.0%)
Intercurrent death not due to malignant disease	0 (0.0%)	1 (0.6%)
Other	1 (0.6%)	3 (1.7%)
Within 30 days of last study treatment	8 (4.6%)	22 (12.2%)
Progression of disease	1 (0.6%)	3 (1.7%)
Toxicity	4 (2.3%)	11 (6.1%)
Infection not due to protocol treatment	1 (0.6%)	0 (0.0%)
Intercurrent death not due to malignant disease	1 (0.6%)	1 (0.6%)
Other	1 (0.6%)	7 (3.9%)
More than 30 days after last study treatment	107 (61.5%)	116 (64.1%)
Progression of disease	88 (50.6%)	103 (56.9%)
Infection not due to protocol treatment	3 (1.7%)	4 (2.2%)
Intercurrent death not due to malignant disease	5 (2.9%)	1 (0.6%)
Other	11 (6.3%)	7 (3.9%)
Missing	0 (0.0%)	1 (0.6%)

SP = safety population; TPF = Taxotere + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients

^a Patient 47 (randomized in TPF group) died from progressive disease but date of death is UKFEB2001, by convention the date is set to 01FEB2001

^b Death within 60 days from first administration of study treatment is also included in any of the other "dead" category (within 30 or more than 30 days from last administration of study treatment)

Deaths within 30 days of last study treatment:

The cases of death from non-malignant cause were more frequent in the PF treatment group (19 patients, 10.5%) than in the TPF treatment group (7 patients, 4.0%). Toxic deaths occurred in 4 patients (2.3%) in the TPF treatment group and 11 patients (6.1%) in the PF treatment group. Infection was the most common AE leading to death within 30 days of the last study treatment, with 3 patients in the TPF treatment group and 11 patients in the PF treatment group. In most cases, the infection was considered by the investigator to be related to treatment.

Deaths more than 30 days after last study treatment:

223 patients (62.8%) died at least 30 days after the last study treatment: 107 in the TPF treatment group (61.5%) and 116 in the PF treatment group (64.1%). The major cause of late death was disease progression. The other causes of deaths that involved 32 patients (TPF: 19 patients; PF: 13 patients) were distributed as follows: infection not due to protocol treatment (TPF: 3 patients; PF: 4 patients), other associated chronic disease (TPF: 1 patient; PF: 1 patient), pulmonary embolism (PF: 1 patient), intercurrent death not due to malignant disease (TPF: 5 patients; PF: 1 patient), other (TPF: 10 patients; PF: 5 patients), and 1 patient in PF for whom cause of death was missing. There were no deaths more than 30 days after the last study treatment that were related to study treatment.

Withdrawal due to adverse events

Discontinuation of chemotherapy due to AEs occurred in 6.2% of TPF-treated patients and 11.6% of PF-treated patients. The most frequent AE that caused study discontinuation was altered hearing, with all instances in the PF treatment group (2.8%).

Laboratory safety data

Hematological evaluation

- Anemia of any grade occurred frequently (88% of patients overall), and the incidence was comparable for both treatment groups. Grade 3-4 anemia occurred in 9.2% of patients in the TPF group and 13.8% in the PF group.

- Leukopenia of any grade occurred in 91.4% of patients in the TPF group and 76.2% of patients in the PF group regardless of the use of G-CSF. Grade 3/4 leukopenia was also more frequent in the TPF group (41.4%) than in the PF group (23.2%).

- Neutropenia occurred was more frequent among patients in the TPF group (93.1%) than in the PF group (86.7%). Grade 3/4 neutropenia was also more frequent in the TPF group (76.3%) than in the PF group (52.8%), regardless the use of G-CSF.

Prophylactic G-CSF was given to a total of 31 evaluable patients (8.7%), limiting assessment of benefit. The incidence of grade 4 neutropenia was similar with or without G-CSF.

- Thrombocytopenia was higher in the PF treatment (47.0%) than in the TPF group (23.6%). Grade 3/4 thrombocytopenia was also more frequent in the PF group (18.2%) than in the TPF group (5.2%).

Reported haematological toxicity is not unexpected due to the haematological safety profile of docetaxel, cisplatin and 5FU. The tabulation below summarizes the different haematological results in both treatment groups.

<i>Adverse event</i>	<i>TPF Regimen (N = 174)</i>	<i>PF Regimen (N = 181)</i>
<i>Anemia</i>		
<i>All</i>	155 (89.1%)	159 (87.8%)
<i>Grade 3-4</i>	16 (9.2%)	25 (13.8%)
<i>Leukopenia</i>		
<i>All</i>	159 (91.4%)	138 (76.2%)
<i>Grade 3-4</i>	72 (41.4%)	42 (23.2%)
<i>Neutropenia</i>		
<i>All</i>	161 (93.1%)	156 (86.7%)
<i>Grade 3-4</i>	132 (76.3%)	95 (52.8%)
<i>Grade 4</i>	85 (49.1%)	43 (23.9%)
<i>Thrombocytopenia</i>		
<i>All</i>	41 (23.6%)	85 (47.0%)
<i>Grade 3-4</i>	9 (5.2%)	33 (18.2%)

Serum chemistry

The parameters of any grade reported with a difference >10% were hypomagnesemia for the TPF group and creatinine increased for the PF group. Few patients had grade 3/4 abnormalities in serum chemistry parameters. The serum chemistry abnormalities were generally comparable between treatment groups.

Regarding Hypocalcemia, the number of patients who presented a hypocalcemia any grade was comparable in both groups (19.8% vs 18.8%). Nevertheless, Grade 3-4 and Grade 4 Hypocalcemia were higher in the TPF arm compared to the PF arm: 8 patients (4.8%) vs 4 (2.3%) for Grade 3-4 and 6 patients (3.6%) vs 2 (1.1%) for Grade 4.

Specific Safety Issues

Neutropenic infection and febrile neutropenia

Primary prophylaxis with antibiotics was required only in the TPF treatment group. 164 patients from the TPF group (94.3%) and 12 patients from the PF group (6.6%) received primary prophylaxis with antibiotics.

Secondary infection prophylaxis was required for both treatment groups in the event of a previous febrile neutropenia/infection episode or prolonged neutropenia grade 4 (≥ 7 days) or in case of delayed neutropenia recovery (≥ 28 days).

The use of G-CSF in treatment of severe neutropenia was low and similar in both treatment groups.

In correlation with the increase incidence of neutropenia grade 4 in the TPF treatment group, there was a higher number of patients with febrile neutropenia (TPF: 5.2%; PF: 2.2%) or neutropenic infection (TPF: 13.9%; PF: 8.3%).

Four patients in the TPF treatment group and 6 patients in the PF treatment group died due to neutropenic infection. All 6 deaths due to infection or subsequent multi-organ failure in the PF treatment group occurred within 30 days of chemotherapy and were considered related to the chemotherapy. The same was true of only 2 of the 4 neutropenic infections in the TPF treatment group: Patients 00202 and 00236 died of infection not due to protocol treatment more than 30 days after the last study treatment.

Discussion on Clinical Safety

The safety profile of the TPF regimen is in accordance with what was expected, and is acceptable. The global toxicity in the TPF arm appears to be better tolerated as compared to the PF arm.

Skin toxicity, whatever the Grade of events, was higher in the TPF arm compared to PF arm. On the other hand, gastrointestinal toxicity was higher in the PF arm as compared to the TPF arm.

Hypersensitivity and ocular reactions, which represent well-known toxicities of docetaxel, are mostly reported in the TPF arm compared to the PF arm [(6.3% vs 2.8%) and (4.6% vs 1.7%)].

There were more reports of alopecia, lethargy, diarrhea, taste and sense of smell altered in the TPF arm and more stomatitis, nausea, and vomiting in the PF arm.

Frequencies of serious adverse events during chemotherapy are comparable between the two treatment groups.

Although frequencies of fever in absence of infection (TPF: 5.7%, PF: 2.8%), febrileneutropenia (TPF: 5.2%, PF: 2.2%) and Grade 3-4 neutropenia (TPF: 76.3%, PF: 52.8%) were higher in the TPF arm compared to the PF arm, the frequency of death due to infection was higher in the PF arm. The positive role of prophylaxis antibiotherapy in the TPF arm cannot be ruled out.

The frequency of death within 30 days of last study treatment was higher in the PF arm as compared to the TPF arm (12% vs 4.6%), with a higher number of toxic deaths in the PF arm as compared to the TPF arm (11(6.1%) vs 4 (2.3%)). With reference to toxic death: 2/4 cases in the TPF arm and 9/11 in the PF arm were due to infection and/or sepsis. Most of the cases of infection leading to death appeared during cycle 1 of chemotherapy treatment (2/2 in TPF arm; 4/9 in PF arm).

The overall incidence of severe infections that were not a complication of a neutropenia were not different in the PF arm as compared to the TPF arm (7.7% and 8.6%, respectively). Therefore, the higher rate of toxic deaths within 30 days of last chemotherapy in the PF control arm than in the TPF tested arm could not be clearly explained.

No scientific rationale supports the use and the benefit of prophylactic antibiotic therapy in the TPF arm. Indeed at the initiation of study TAX323, based on limited data from the non-controlled phase II study, TAX 017, including TPF regimen in subjects with SCCHN, it was deemed appropriate to include mandatory, broad-spectrum, oral antibiotic prophylaxis (ie, ciprofloxacin) for all subjects randomised to receive TPF. As discussed above, in study TAX323, the incidence of clinical significant infectious episodes is similar between TPF and PF and even higher in TPF arm. Treatment-related neutropenic infection and febrile neutropenia were reported more frequently in the TPF treatment arm compared to PF: 11.0% and 5.2% compared to 5.6% and 2.2% per patient, respectively. As the compliance with antibiotic prophylaxis was high, there are no results for TPF regimen without ciprofloxacin from this study. As most oncology organizations do currently not recommend antibiotic prophylaxis in this setting, the CHMP would not recommend compulsory prophylactic antibiotic therapy for TPF.

Relatively higher proportions of elderly patients experienced febrile neutropenia or neutropenic infections. Because of the small number of patients aged 65 and above, no conclusion could be drawn from this study.

Regarding deaths more than 30 days after last study treatment: death was reported as other cause than disease progression for 19 patients in TPF arm and 13 in PF arm. Among the 19 cases of death in the TPF arm, 15 were reported as “Other” or “Intercurrent death not due to malignant disease”. The CHMP agrees that among these 15 death cases, no cases evoked suspected toxic death related to chemotherapy.

Altered hearing led to discontinuation in (5/181) patients in the PF arm. This represents the most frequent adverse event leading to discontinuation in the PF arm.

Regarding the TPF arm, 11 patients presented adverse events leading to discontinuation. Among them, 3 cases concerned myocardial ischemia (1.7%) are reported as serious related adverse events in the TPF arm. In two cases, the patients did not present any cardiovascular history. In the remaining case, the patient presented a history of hypertension, COPD, and hypercholesterolemia. All the cases were considered as probably related to regimen by the investigator.

The ADR “myocardial ischemia” has been added in section 4.8 of the SPC of docetaxel under Taxotere in combination with cisplatin and 5-FU. The CHMP agree to only mention the risk of cardiac ischemia in section 4.8 at this point in time. However, the risk should be monitored as part of future PSURs.

Benefit-risk assessment

Patients with inoperable locally advanced squamous cell carcinoma of the head and neck (SCCHN) have a poor prognosis. Treatment of advanced SCCHN is complex and involves not only chemotherapy but also radiotherapy and surgery. The role of induction chemotherapy (i.e., neoadjuvant therapy) in the treatment of locally advanced SCCHN remains controversial despite evidence that integrating chemotherapy into the treatment plan of locally advanced disease can lead to organ preservation and improved survival of patients with resectable and unresectable disease.

This is the second application for a type II variation to extend the indications of TAXOTERE in the “*induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck in combination with cisplatin and 5-fluorouracil*”, is supported by a large, well-managed and well-analysed pivotal phase III trial, XRP6976F-323/EORTC 2971 (EFC6042). This study assessed the benefit of induction chemotherapy followed by conventional radiotherapy.

Patients were randomized to receive either:

- test group: docetaxel plus cisplatin plus 5-FU (TPF) followed by locoregional radiation therapy
- control group: cisplatin plus 5-FU (PF) followed by locoregional radiation therapy

Randomization was stratified upon 2 factors: the primary tumor site (oral cavity versus oropharynx versus hypopharynx versus larynx) and the center (i.e. institution).

The comparator regimen is well recognised. At the time of study initiation, reference chemotherapy treatment in this neoadjuvant setting of SCCHN was cisplatin 100 mg/m² plus 5-fluorouracil 1000 mg/m² (Paccagnella A et al. 1994). Therefore the control arm is acceptable. However, it remains unclear how TPF compares to the current standard treatment, chemoradiotherapy (CRT) regarding efficacy and safety.

In the TPF arm only, patients had to receive prophylactic antibiotic therapy.

No scientific rationale supports the use and the benefit of prophylactic antibiotic therapy in the TPF arm. At the time of the initiation of study TAX323, based on limited data from the non-controlled phase II study TAX 017, including TPF regimen in subjects with SCCHN, it was deemed appropriate to include mandatory, broad-spectrum, oral antibiotic prophylaxis (i.e., ciprofloxacin) for all subjects randomised to receive TPF. In TAX017 lower rates of treatment-related infections and fever in the absence of infection were observed in the cohort that received prophylactic antibiotic therapy.

In study TAX323, the incidence of clinical significant infectious episodes is similar between TPF and PF and even higher in the TPF arm (treatment-related neutropenic infection and febrile neutropenia were reported more frequently in the TPF treatment arm compared to PF: 11.0% and 5.2% compared to 5.6% and 2.2% per patient respectively).

Most oncology organizations do not seem to recommend antibiotic prophylaxis in this setting at present. Accordingly, the CHMP does not recommend compulsory prophylactic antibiotic therapy for TPF.

With reference to demographic and tumor characteristics at baseline, the two treatment groups are comparable: most patients were men (89.7%), the median age was 53 years, with a range of 30 to 70 years. All patients except 1 in the TPF treatment group had WHO performance status of 0 or 1.

The most frequent tumor site was the oropharynx (46.1% of patients). The most frequent clinical TNM stage in both treatment groups was T4 / N2.

The vast majority of patients received chemotherapy and radiotherapy as outlined in the protocol.

Surgery was performed at the discretion of the local multidisciplinary team.

More patients in the TPF arm had surgery during the study: 45 patients (25.9%) in the TPF treatment group and 27 patients (14.9%) in the PF.

The median relative dose intensity is above 0.90 in both study arms.

A majority of patients in both treatment groups completed chemotherapy as per protocol (as intended): 70.1% in the TPF treatment group and 61.9% in the PF treatment group. Completion of chemotherapy as per protocol "includes patients who completed chemotherapy either after 2 cycles or after 4 cycles".

In the TPF treatment group, 137 patients (78.7%) received 4 cycles of chemotherapy and in the PF treatment group 119 (65.7%) patients received 4 cycles.

Chemotherapy was discontinued in 52 (29.4%) of patients in the TPF treatment group and in 68 (37.6%) patients in the PF treatment group. In both treatment groups, the most frequent reasons for discontinuation from study medication were progressive disease (TPF: 24 patients, 13.6%; PF: 20 patients, 11.0%), AEs (TPF: 11 patients, 6.2%; PF: 21 patients, 11.6%) and death (TPF: 6 patients, 3.4%; PF: 12 patients, 6.6%).

As requested, the MAH performed an analysis on the patient group that completed chemotherapy as intended. Both subgroup OS and PFS analyses are consistent with the primary analyses favouring the TPF arm. The benefit of TPF seems not to be linked to a suboptimal dosing of PF.

Clinical efficacy results of study TAX323 are convincing in terms of significantly decreased risk for progression (primary criterion PFS) and survival benefit (secondary criterion). These results are clinically relevant and reached statistical significance:

Primary efficacy analysis was a comparison of PFS adjusted for prognostic factors in the ITT population at the end of the study using a Cox proportional hazards model.

Treatment with TPF was associated with a 30% progression risk reduction compared to treatment with PF, when adjusting for the prognostic factors (WHO PS, primary tumor site): HR of 0.70 (95% CI: 0.55-0.89; P = 0.0042).

Median PFS was higher in the TPF treatment group (11.4 months, 95% CI: 10.1-14.0) than in the PF treatment group (8.3 months, 95% CI: 7.4-9.1), (HR 0.72, 95% CI: 0.57-0.92; log-rank test, P = 0.0073).

About 80% of patients reported a locoregional relapse and about 9% reported a distant relapse. The analyses of PFS by type of relapse, report a Hazard Ratio similar to the overall PFS analysis i.e., still in favor of TPF arm. (HR for Overall PFS: 0.72; HR for locoregional PFS: 0.74; HR for distant PFS: 0.73). A higher proportion of relapses (recurrent/local or metastasis) was reported in the TPF tested arm. This could be explained by the higher rate of “undefined” relapses in the PF control arm (10.3% vs 5%).

The originally planned external review of responses was cancelled, as PFS was the primary endpoint of the study (Protocol Amendment 2). It is well recognised in this population that the review of radiologic images alone is not sufficient for adequate tumor assessment because of many confounding factors such as inflammation, oedema, and large necrotic lymph nodes. The response assessment of locally advanced SCCHN is mostly clinical and in an open trial, a blinded assessment would have been preferable. In order to provide unbiased results, the independent “blinded” review of images could have been changed into an Independent Clinical Review Committee (ICRC).

The study was conducted in collaboration with a recognised institution, EORTC, and an Independent Data Monitoring Committee (IDMC) was established.

According to the Guideline on the evaluation of anticancer medicinal products in man (CHMP/EWP/205/95/Rev. 3) acceptable primary endpoints for phase III therapeutic confirmatory studies should be time related. For the tumor entity SCCHN the combination of primary endpoint PFS with the key secondary endpoint overall survival is considered acceptable to assess the clinical benefit of TPF treatment.

Secondary analyses supported the conclusions of the primary analyses:

- median time to death (TPF: 18.6 months; PF: 14.5 months) showed a 28% risk reduction of death as compared to PF treatment group and a 3-years survival rate estimate of 37.9% for TPF (versus 26.3 for PF);
- best overall response to study treatment (chemotherapy + radiotherapy) (TPF: 72.3%; PF: 58.6%),
- duration of response (TPF: 15.7 months; PF: 11.7 months), and
- time to treatment failure (TPF: 10.3 months; PF: 7.3 months) were all in favour of TPF as compared to PF.

All of these differences are statistically significant.

Analyses for PFS and OS according to the stratification factors by Cox model, including tumour localisation and center, and tumour localisation and geographical region respectively, were performed. HR adjusted for the stratification factors are consistent with the overall primary analyses results presented. The treatment effect is similar between small and large centers and in accordance with the overall primary PFS and OS analyses.

Thus, clinical efficacy of docetaxel associated with cisplatin/5-FU treatment has been demonstrated with reference to PFS, OS, and ORR. Overall efficacy data are considered sufficiently robust to support regulatory approval of TPF in the induction treatment of inoperable SCCHN.

Two QoL questionnaires and 3 instruments for the measurement of clinical benefit were used. Compliance with the instruments decreased over time, it was unacceptably low for the QLQ-H&N35 questionnaire partly due to the fact that questionnaire translations were not available for some countries. For quality of life the predefined analysis of the EORTC QLQ-C30 showed a significant benefit for TPF treatment. Results were similar for the Performance Status Scale for Head and Neck and an exploratory analysis of the deterioration of the WHO performance scale. These results may reflect those of the efficacy endpoints. At least an independent deterioration of quality of life by the experimental treatment can be excluded.

Pain intensity improved during treatment in both groups indicating adequate pain management in both treatment groups.

From the point of view of safety, as expected for this type of combination chemotherapy, nearly all patients in both treatment arms experienced treatment related adverse events. The incidences for severe TEAEs (grade 3-4 and grade 4 respectively) and serious TEAEs were comparable between the treatment groups.

Generally the pattern of the reported AEs is as expected for the used medicinal products. The TEAEs that were more commonly reported with TPF compared with PF attribute mostly to the addition of docetaxel: neutropenia, neutropenic infection, lethargy, diarrhoea, fluid retention, neurosensory, sense of smell/taste altered. However, thrombocytopenia, nausea, vomiting, anorexia and weight loss were observed more frequently with PF, which may reflect the higher dose intensity of cisplatin.

No new type of TEAE was identified in the studies. The tolerance of radiotherapy was not impaired by the new combination.

Fewer patients withdraw from the trial due to adverse events in the TPF treatment group. It is encouraging that the experimental treatment was associated with fewer deaths within 30 days of study treatment and fewer deaths due to infections. The routine antibiotic prophylaxis in the TPF group may account to this difference.

The application also included two Phase I/II studies (TAX 017 and TAX 708) in SCCHN investigating two different doses of cisplatin and the combination docetaxel, cisplatin, and 5-fluorouracil. These studies had a similar design and were performed in the target population of patients with advanced previously untreated SCCHN in Europe and the US.

These studies were part of the previous submission in 2000. No updated data are provided in this second submission.

Differences in drug schedules and patient populations may explain the differences observed in efficacy and safety results. Consequently, the heterogeneous results rendered the analysis particularly difficult. The data could only be considered as indicative of an activity of TPF in this medical setting, but not sufficient to support an extension of indication of Taxotere. For this second submission, study TAX017HN could be considered as the basis for dose schedule selection for study TAX323.

The MAH sponsors another US phase III study in a similar indication, TAX 324, investigating induction chemotherapy (TPF vs PF) followed by concomitant radio-chemotherapy. From the point of view of current clinical practice, the design of study TAX324 is interesting.

The MAH has committed to submit the final clinical study report of study TAX324 as soon as it becomes available.

Reference was also made to the pharmacokinetic interaction study, XRP6976E/1001, submitted and assessed within variation II67 for the gastric adenocarcinoma indication.

The primary objective of this study was to determine in a randomized, cross-over setting (each patient being his own control), if there was any clinically significant pharmacokinetic interaction between docetaxel (Taxotere) 75 mg/m², cisplatin 75 mg/m², and 5-fluorouracil (5-FU) 750 mg/m²/day for 5 days. Study, XRP6976E/1001 included 15 patients with solid tumors who received either TPF at cycle 1 and TP at cycle 2, or TP at cycle 1 and TPF at cycle 2.

Study XRP6976E/1001 led to include the following information in the section 5.2 (Pharmacokinetic Properties) of the SPC "The combined administration of docetaxel, cisplatin and 5-fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug."

In conclusion, the CHMP considers that the Benefit Risk balance of docetaxel in combination with cisplatin and 5-fluorouracil as induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck, is clearly positive.

- CONCLUSION

On 21 September 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.