European Medicines Agency

London, 5 December 2007
Product name: **DOCETAXEL WINTHROP**
Procedure No. **EMEA/H/C/808/II/01**

SCIENTIFIC DISCUSSION

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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

Docetaxel Winthrop 20 and 80 mg concentrate and solvent for solution for infusion (INN: docetaxel) was granted a Marketing Authorisation (MA) in April 2007.

Docetaxel Winthrop is an antineoplastic agent (ATC code: L01CD02) that blocks cells in the M phase of the cell cycle by interfering with microtubule structure and function. Docetaxel acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly, which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments.

Docetaxel Winthrop is indicated for the treatment of:

Breast cancer
- in combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node- positive breast cancer.
- in combination with doxorubicin is indicated 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 is indicated 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 is indicated 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 is indicated 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 is indicated for the treatment of patients with hormone refractory metastatic prostate cancer.

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

Head and neck cancer
- 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.

This variation concerns an extension of indication for Docetaxel Winthrop (docetaxel) in head and neck cancer.

Head and neck cancer

Squamous cell cancer of head and neck (SCCHN) represents 5% of newly diagnosed cancers in adult patients. Worldwide, more than 600 000 new cases are projected annually. There are wide differences

in incidence according to geographical region and gender. Excessive tobacco and alcohol consumption, and nutritional deficiencies are the risk factors for SCCHN.
Various anatomical sites with specific features can be differentiated: cancer of lip and oral cavity, oropharyngeal cancer, hypopharyngeal cancer, laryngeal cancer, nasopharyngeal cancer and cancer of paranasal sinus and nasal cavity.
SCCHN is a potentially curable malignancy when diagnosed at an early stage. Most patients present with advanced loco-regional disease, defined as either stage III (T3N0M0 or T1-3N1M0) or stage IV (T4N0-1M0 or T1-4N2-3M0).
Prognosis has remained poor for this group of patients. Between 50% and 60% will develop loco-regional recurrence within 2 years, and 20% to 30% will develop distant metastases.

The terms “unresectable” or "inoperable" SCCHN are not clearly defined. In general, SCCHN is considered as unresectable if all gross tumour cannot be removed on anatomic grounds or if local control cannot be achieved after an operation. Definitive surgery for intermediate- or advanced-stage disease within the larynx, hypopharynx, and oropharynx may lead to profound functional morbidity. The experience of the surgeon and the support available strongly influence recommendations for treatment.
Patients having resectable tumours but who could also be adequately treated without surgery represent a very important group. In these individuals, definitive treatment with radiation therapy (RT) alone or in combination with chemotherapy may represent a preferable approach to resection in the interest of organ preservation.

Advanced SCCHN includes newly diagnosed but unresectable disease, recurrent disease, and metastatic disease. The treatment goal for patients with newly diagnosed but unresectable disease is cure. In the past decade clinical trials investigated alternative radiotherapy fractionation schedules, concurrent chemoradiotherapy, and novel radiosensitizers in patients with unresectable disease. For patients with a performance status (PS) of 0 or 1, the widely used treatment for newly diagnosed but unresectable disease is cisplatin- or carboplatin-based chemotherapy and radiotherapy. Until now there has been no definitive general agreement on the benefit of adding induction chemotherapy to loco-regional therapy (radiation alone or concomitant chemo-radiation). The objective of induction chemotherapy (neoadjuvant chemotherapy) is to improve loco-regional disease control and eradicate potential distant metastases. Several induction chemotherapy trials have been conducted with different drugs and schedules, with mixed results. A meta-analysis showed a small survival benefit with cisplatin and 5-fluorouracil (PF) induction chemotherapy. Induction chemotherapy with PF (Cisplatin (p) 100 mg/m² day 1 and 5-FU (F) 1000 mg/m² by continuous infusion day 1-5) has become a standard regimen for patients with locally advanced head and neck cancer.

Scope of the variation

The scope of variation EMEA/H/C/0808/II/01 is an extension of the current indication in head and neck cancer which was approved based on the European TAX 323 study. In TAX 323, only inoperable patients with locally advanced squamous cell carcinoma of the head and neck had been included (stage III-IV, all sites except nasopharynx, nasal and paranasal cavity). Inoperability was determined by a multidisciplinary team and was mainly due to unresectability. TAX 323 excluded technically operable patients who refused surgery and patients for organ preservation.

The MAH has now applied to broaden the head and neck cancer indication as follows:
“Docetaxel Winthrop (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.”

This application is based on the results of the US phase III study TAX 324, comparing induction treatment with Docetaxel plus Cisplatin plus 5-Fluorouracil (TPF) to treatment with Cisplatin plus 5-Fluorouracil (PF). Both arms were followed by treatment with chemo-radiotherapy. The population of patients included those who are technically unresectable, those with low probability of surgical cure (<20% chance of cure), and those who could be resected but wanted to maintain function (organ preservation) each group comprising approximately one third of the overall patient population.

Further changes refer to SPC sections 4.2 posology and method of administration, 4.8 undesirable effects, 5.1 Pharmacodynamic properties. The Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to make minor editorial changes to the SPC and to update the annexes in line with the latest QRD template.

Non clinical aspects

For the head and neck adenocarcinoma indication, no additional specific non clinical data have been provided, which is acceptable. All the previously submitted non clinical studies support this extension of indication, especially the 10-cycle toxicity and toxicokinetic studies undertaken in rat and dogs, which were conducted with the same regimen of administration as in the claimed indication.

Clinical aspects

GCP compliance

The clinical programme described in this report was conducted in accordance with Good Clinical Practice (GCP) as required by the International Conference on Harmonization Guideline for Good Clinical Practice (ICH E6), 1 May 1996, in agreement with the Declaration of Helsinki and standard operating procedures for clinical investigation and documentation in effect at the sponsor worldwide. The pivotal study was also carried out according to local legal requirements.
This application has been formulated in compliance with the "Note for guidance on evaluation of anti-cancer medicinal products in man" CPMP/EWP/205/95 Rev 2, July 2003.

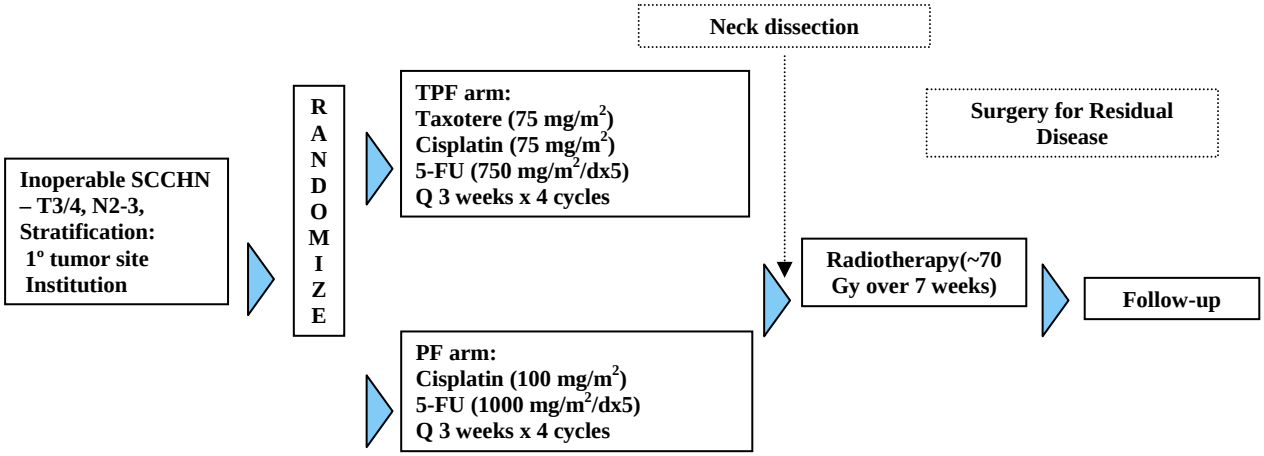
Clinical Pharmacology

Reference is made to the pharmacokinetic interaction study, **TAX 1001**, submitted previously as part of variation II/67 for the gastric adenocarcinoma indication. TAX 1001 was a pharmacokinetic interaction study of 75 mg/m² of docetaxel plus cisplatin 75 mg/m² and 5-FU 750 mg/m²/day for 5 days in the treatment of patients with recurrent or metastatic solid tumours.
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 docétaxel, cisplatin and 5-fluorouracil.
Blood sampling procedures as well as analytical methods were adequate. The results did not suggest any interaction between drugs. Due to the study design the results provided information mostly on a low intrapatient variability for cisplatin and docetaxel. It would have been more appropriate to study the two treatments involved in the phase III trials (i.e. TPF versus PF). Despite that, pharmacokinetics interaction between docetaxel and 5-fluorouracil or cisplatin could be reasonably excluded due to the respective way of elimination for each drug:
- docetaxel metabolised by CytP450 3A,
- cisplatin: mainly urinary elimination, and nearly irreversible binding to plasma proteins,
- 5-fluorouracil catabolised by the dihydropyrimidine dehydrogenase.

Clinical efficacy

Summary of Study TAX 323 *(submitted as part of the initial Marketing Authorisation Application)*

TAX 323 was an international, multicenter, open-label, randomized phase III study, which assessed the benefit of induction chemotherapy (TPF vs. PF) followed by conventional radiotherapy in patients with inoperable locally advanced SCCHN.



The primary objective was to compare progression-free survival (PFS) in the 2 treatment groups, and the main secondary objective was to compare Overall survival (OS). Patients received 4 cycles of chemotherapy every 3 weeks either:
- **Test group (TPF):** Docetaxel 75mg/m^2 Day 1, cisplatin 75 mg/m^2 Day 1, and 5-FU 750 mg/m^2/day on Days 1-5, or
- **Control group (PF):** Cisplatin 100 mg/m^2 Day 1, and 5-FU 1000 mg/m^2/day on Days 1-5.

Induction chemotherapy was followed by radiotherapy delivered, either with a conventional fraction regimen, or with an accelerated/hyperfractionated regimen, for a total dose of 70 to 74 Gray, respectively. Surgery to either the primary tumour or neck was permitted after chemotherapy and prior to initiation of radiation for patients without disease progression. Surgeries after radiotherapy were performed at the discretion of the local multidisciplinary team. Patients were followed until death.

The ITT population included 358 patients. Treatment groups were comparable at the baseline for demographic and clinical characteristics. The most frequent tumour site was the oropharynx (46.1%) and the most frequent stag was T4/N2. The results of study TAX 323 are summarized in table 1.

Table 1- Summary of efficacy (ITT population) in TAX323

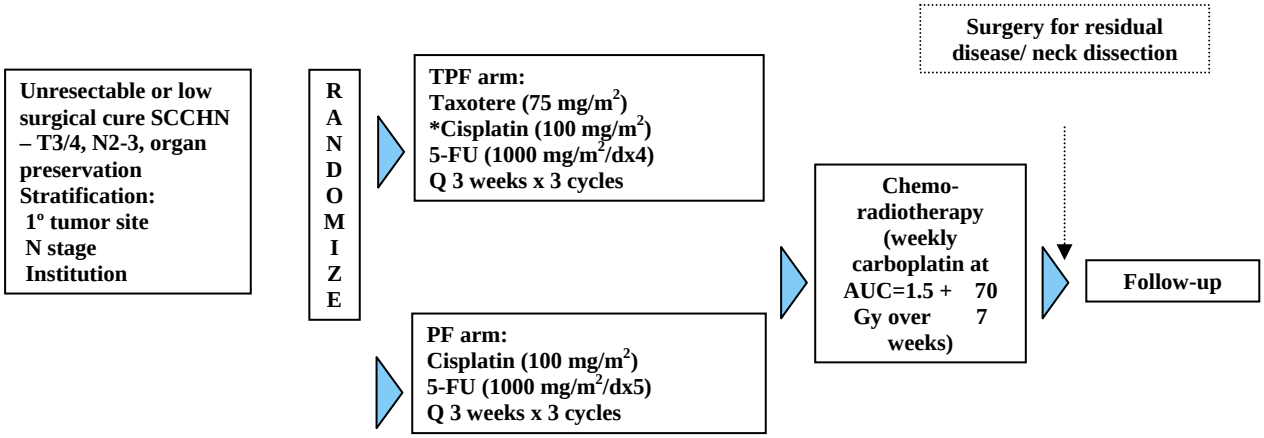
Endpoint	TPF N=177	PF N=181
Median progression-free survival (months)	11.4	8.3
(95% CI)	(10.1-14.0)	(7.4-9.1)
Adjusted Hazard ratio	0.70	
(95% CI)	(0.55-0.89)	
P-value [a]	0.0042	
Median survival (months)	18.6	14.5
(95% CI)	(15.7-24.0)	(11.6-18.7)
Hazard ratio	0.72	
(95% CI)	(0.56-0.93)	
P-value [b]	0.0128	

[a] Cox proportional hazards model
[b] Log-rank test

Study TAX 324

- **Methods**

TAX 324, investigated induction chemotherapy (TPF vs. PF) followed by concomitant radio-chemotherapy.



TAX 324 was a multicenter, open-label, randomized, stratified, phase III study comparing two combination therapy regimens as induction treatment before chemoradiotherapy for locally advanced SCCHN. Patients were randomized to receive either the triple test therapy (TPF) or control treatment (PF), followed by chemoradiotherapy in both groups.

Randomization was stratified upon 3 factors:
- the primary tumor site (oral cavity versus oropharynx versus hypopharynx versus larynx);
- the N stage (N0-1 versus N2-3);
- the center.

The first patient was randomized on 21 May 1999; the clinical cut-off for overall survival was the 3 December 2005.

The primary objective was to compare the overall survival (OS) after treatment with the test tri-therapy (TPF: docetaxel plus cisplatin and 5-FU) or the control treatment (PF: cisplatin plus 5-FU) followed by chemoradiotherapy in patients with locally advanced SCCHN.

The secondary objectives were to evaluate and compare: progression free survival (PFS), improvement of local symptoms; time-to-treatment failure (TTF); QoL; clinical complete response rate (CRR) and ORR (ORR = PR+CR) after induction chemotherapy and after loco-regional therapy (chemoradiotherapy); duration of response (CR and CR+PR); toxicity; and to evaluate the relationship of tumor markers and response to therapy.

- **Protocol amendments**

Five protocol amendments were performed:
- Amendment 1 (March 1999): clarifications of the dose modification schedule, modification of the dosing regimen.
- Amendment 2 (March 2000): addition of the following to secondary objectives: evaluate the relationship of tumor markers and response to therapy. An effort was to be made to reduce center variability in radiotherapy practices by employing a centralized reporting and consultation service; clarification of procedures for cytological assessment of tumor type and tumor response and clarified

procedures for secondary analysis of tumor markers; of criteria for assessing toxicity and late radiation toxicity; of criteria and timing for removal of patients from therapy;
- Amendment 3 (May 2001): changed the primary objective to OS, made PFS the main secondary endpoint, added complete response rate (CRR) after induction chemotherapy and overall response rate (ORR = partial response rate + complete response rate) after induction chemotherapy and after chemoradiotherapy as secondary endpoints, and removed organ preservation as a secondary endpoint.
- Amendment 4 (March 2002): allow a pharmacokinetic study in selected patients (n=24) to evaluate pharmacokinetics in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) who receive docetaxel, cisplatin, and 5-fluorouracil (5-FU) (TPF).
- Amendment 5 (September 2003): increasing of the total sample size to 538 patients, to compensate for 38 patients excluded from the primary efficacy analysis.

- **Study participants**

The main inclusion criteria were:
- Histologically and cytologically proven SCCHN.
- Primary tumor sites eligible: oral cavity, oropharynx, hypopharynx or larynx. (exclusion of tumors of the nasal and paranasal cavities and nasopharynx)
- Stage III and IV without metastases
- Uni- or bidimensionally mesurable lesion
- Tumors considered as inoperable:
  Technical unresectability
  Physician's selection based on low surgical curability : all T3-4 stages, all N2-3 stage including T1N2
  Patient for organ preservation
- No previous chemotherapy or radiotherapy for any reason and no surgery for SCCHN (other than biopsy)
- Age ≥ 18 years
- WHO performance status of 0 or 1
- Adequate renal, hepatic and bone marrow functions.

- **Treatment regimen**

Induction treatment:

Patients were to receive up to 3 cycles of induction chemotherapy at 3 week intervals.
- Test group (TPF):
Docetaxel 75 mg/m^2, as a 1-hour intravenous infusion, Day 1
Cisplatin 100 mg/m^2, administered as a 30-minute to 3-hour intravenous infusion on Day 1.
5-FU was administered after cisplatin as a continuous intravenous infusion at 1000 mg/m^2 per day Day1 to 4.
- Control group (PF):
Cisplatin 100 mg/m^2, administered as a 30-minute to 3-hour intravenous infusion on Day 1
5-FU continuous intravenous infusion at 1000 mg/m^2 per day Day 1 to 5.

Locoregional treatment:

Chemoradiotherapy: chemoradiotherapy began 3 to 8 weeks after the start of the last cycle of induction chemotherapy. Patients had to fulfill the criteria to eligible for radiotherapy: adequate bone narrow function, complete resolution of mucositis for at least 1 week and healed dental procedures.
- Chemotherapy: Carboplatin was to be given weekly as a one-hour infusion for a maximum of 7 doses during radiation. The weekly carboplatin dose was to be calculated by the area under the curve (AUC) estimate of Calvert (AUC = 1.5) and was to be given on a Monday, Tuesday, or Wednesday prior to the radiation treatment. Carboplatin was not to be administered if radiation was withheld.
- Radiotherapy: The definitive therapy radiation dose to the site of the primary tumor was to be between 70 and 74 Gray in 2 Gray per day fractions delivered continuously 5 days per week with not intended treatment break.

Surgery: Surgery for residual disease at the primary site and/or neck could be considered at any time following completion of chemoradiotherapy. Planned neck dissections were allowed based on the pre-treatment N stage and independent of response during treatment. The usual threshold for a planned neck dissection was N2a or greater disease at baseline.

Prophylactic medications:
Both treatment groups received prophylactic treatment.
TPF arm: dexamethasone 8mg, ciprofloxacin 500 mg twice daily for 10 days starting day 5 of cycle
Both arm: anti-emetics, G-CSF secondary prophylaxis allowed.

- **Endpoints**

Primary: Overall survival (OS)

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

Secondary: Progression-free survival (PFS), Time to treatment failure (TTF), Overall response rate (ORR), duration of response and pathological response

PFS was the main secondary endpoint and was calculated from the date of randomization up to the date of progression or the date of death (all reasons), 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).

TTF was calculated from the date of randomization up to the date of failure (progression, recurrence, death, withdrawal due to adverse event, patient's refusal, or lost to follow-up before treatment completion). 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 were censored at the date of the last contact if it occurred before cut-off date; at the cut-off date otherwise.

ORR: the response rate is defined, for each treatment arm, as the percentage of patients in the arm who achieve a complete response (CR) or a partial response (PR) according to the WHO criteria taking into account all assessments performed before any concomitant anti-cancer therapy. Responses calculated by the investigator after induction chemotherapy (ORR-CT), after chemoradiotherapy (ORR-CRT), and overall after study treatment completion (BOR) were used in the analyses.

Of note, the centralised assessment of tumour response was cancelled within protocol amendment 3 because response rate became a secondary endpoint.

Duration of response (PR + CR) was also calculated from the date of randomization up to the first progression in the responders for the whole treatment (induction chemotherapy plus chemoradiotherapy). If progression or death did not occur before the cut-off date/further anti-cancer therapy (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). The duration of complete response (CR) was calculated from the date the complete response was documented up to the documentation of first progression.

Pathological response at the primary site was evaluated by performing an optional biopsy of the primary tumour in patients willing and able to undergo pathological confirmation of the response. Evaluation under anesthesia and optional biopsy were to be performed in responders only (CR and PR). The pathologic complete response rate is the percentage of patients with a negative biopsy for residual disease at primary site among the patients actually biopsied.

Quality of life and clinical benefit
The quality of life assessment was made using the Functional Assessment of Cancer Therapy Head and Neck quality of life instrument (FACT-HN version 4.0), the Performance Status Scale for Head and Neck (PSS-HN), a visual analog scale (VAS) for pain, and the World Health Organization (WHO) performance status score. 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. The consumption of analgesics was also assessed.

Of note, protocol amendment 3 removed organ preservation as a secondary endpoint.

- **Sample size**

For the primary endpoint, OS, a hazard ratio of 0.65 (assumed median OS of 43 months in the TPF treatment group and 28 months in the PF treatment group) could be detected with a 91% power using a 2-sided log-rank test at a 5% significance level with 436 patients (218 per arm) recruited in 30 months. To achieve this statistical hypothesis, the minimum follow-up is 24 months, and a total of 227 events are needed. A maximum of 500 patients were to be recruited (250 per arm), assuming that approximately 15% of patients will be lost-to-follow-up or early dropouts in this study.

PFS was the main secondary endpoint. The null hypothesis of no difference in PFS between treatments was tested using the log-rank test at an overall 2-sided 5% significance level. To achieve approximately 90% power, given a true median PFS for the control arm of 10 vs. 15 months for the test arm, a total of 256 events are needed. With 218 patients per arm enrolled per treatment group, a minimal follow-up of 3 months and 30 months of accrual (i.e., 18 months median follow-up) are needed to achieve this main secondary endpoint.
By protocol amendment 5, the total sample size was increased to 538 patients, to compensate for 38 patients excluded from the primary efficacy analysis.

- **Statistical methods**

Treatment group comparability at baseline was assessed with respect to the following factors:
• Patient characteristics at baseline: age, gender, WHO performance status, reason of inoperability, clinical symptoms, laboratory values.
• Tumour characteristics at inclusion: primary tumour site (oropharynx, hypopharynx, larynx, oral cavity), TNM stage at first diagnosis, combination of T and N stage, histopathological grade, number and type of organs involved, time from first histopathological diagnosis to randomization.

Five different populations were defined:
- The intent-to-treat population (ITT) consisted of all randomised subjects, except 37 patients incorrectly randomised and one patient with GCP compliance issues, analyzed in the treatment group to which they were assigned to by randomisation.
- The chemoradiotherapy safety population (CRSP) consisted of all subjects treated with at least one cycle of study therapy and analysed according to the study medication actually received.
- The radiotherapy safety population (RSP) consisted of all subjects receiving chemoradiotherapy, analysed according to the chemotherapy actually received.
- Patients who satisfied the following condition were evaluable for response: at least two cycles of induction chemotherapy and at least one disease assessment with the same imaging procedure for each lesion as at baseline. If progression occurred before the second cycle, the patient was considered as evaluable and reported as early progression.
- The per protocol population included all ITT patients who were eligible, evaluable for response, and who did not have any major deviation during study are included in the per protocol population.
In order to evaluate the consistency of results, sensitivity analyses were performed on all randomized patients (still excluding the one patient with GCP compliance issues).

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

Time to event data were described using Kaplan-Meier curves and estimates. Confidence intervals were calculated for the median survival time using the method of Brookmeyer and Crowley and for hazard ratios using the Cox model. Groups were compared with log-rank and Wilcoxon tests and in Cox proportional hazards models. For multivariate analysis, the following baseline items were fitted to the model: country, oral cavity primary, oropharynx primary, hypopharynx primary, N stage.
Unadjusted Chi-square tests were used to compare treatment arms for categorical variables unless the expected cell frequency was < 5, in which case an exact test was used, e.g., Fisher's exact test. Confidence intervals (95%) were calculated for binary event rates.
Repeated measures data were analyzed with a method appropriate for the type of data and the missing data mechanism. If data were missing completely at random (MCAR) or missing at random (MAR), normally distributed data were analysed with a mixed model, and ordered categorical data were analysed with a generalized mixed model or with generalized estimating equations. If data are not missing at random (NMAR), a random-coefficient pattern mixture model was used with stratification on the pattern of missing data or the reason for drop-out.

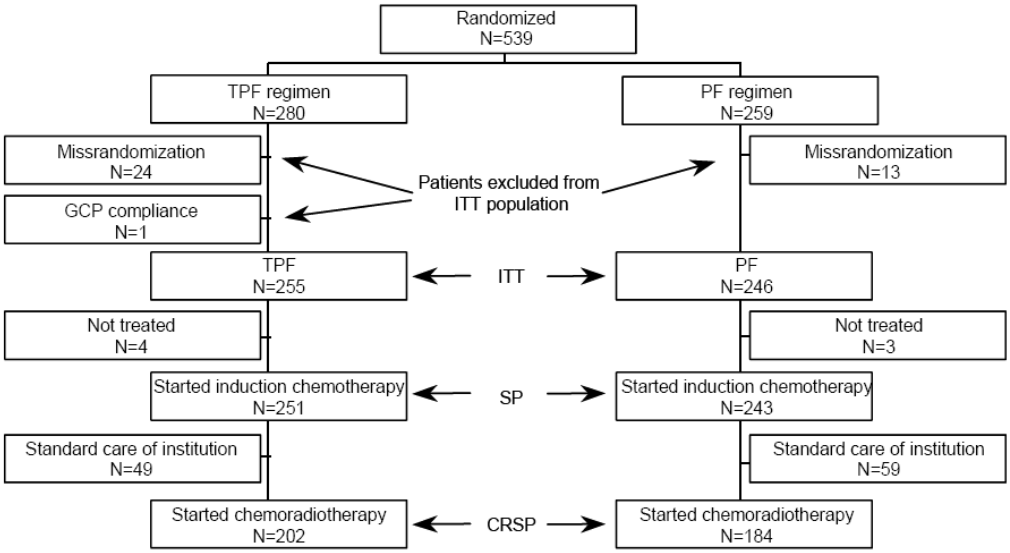
Follow-up
The patients were followed until death or study completion, up to 2 years after the randomization of the last patient.

- **Efficacy results**

There were 539 patients randomized in the study, the ITT population excluded 37 patients incorrectly randomized and 1 patient with GCP compliance. So there were 501 patients randomized, enrolled in 55 sites in 6 countries, over 54.3 months.

Disposition of patients

Figure 1 – Summary flowchart of patient disposition



TPF = docetaxel + cisplatin + 5-FU; PF = cisplatin + 5-FU; ITT = intent-to-treat; SP = safety population; CRSP = chemoradiotherapy safety population

Baseline data
Demographic and tumour characteristics at baseline are shown in tables 2 and 3.

Table 2-Demographics at baseline (ITT)

	RANDOMIZATION GROUP		
	TPF (N=255)	**PF (N=246)**	**ALL (N=501)**
Sex			
Male	215 (84.3%)	204 (82.9%)	419 (83.6%)
Female	40 (15.7%)	42 (17.1%)	82 (16.4%)
Race			
Caucasian	214 (83.9%)	210 (85.4%)	424 (84.6%)
Black	24 (9.4%)	24 (9.8%)	48 (9.6%)
Hispanic	11 (4.3%)	7 (2.8%)	18 (3.6%)
Other	4 (1.6%)	4 (1.6%)	8 (1.6%)
Missing	2 (0.8%)	1 (0.4%)	3 (0.6%)
Age (Years)			
Median	55	56	56
Minimum	38	33	33
Maximum	82	80	82
Age (Years)			
<35	0 (0.0%)	2 (0.8%)	2 (0.4%)
[35,50[	53 (20.8%)	61 (24.8%)	114 (22.8%)
[50,65[	168 (65.9%)	147 (59.8%)	315 (62.9%)
[65,75[	29 (11.4%)	30 (12.2%)	59 (11.8%)
≥ 75	5 (2.0%)	6 (2.4%)	11 (2.2%)
Weight at Cycle 1 (kg)			
Median	73.39	73.92	73.60
Minimum	45.57	45.66	45.57
Maximum	134.70	156.00	156.00
PS WHO			
0	142 (55.7%)	126 (51.2%)	268 (53.5%)
1	113 (44.3%)	117 (47.6%)	230 (45.9%)
Missing	0 (0.0%)	3 (1.2%)	3 (0.6%)

ITT = intent to treat; PS WHO = World Health Organization Performance Status

Table 3-Cancer at first diagnosis (ITT)

	RANDOMIZATION GROUP		
	TPF (N=255)	PF (N=246)	ALL (N=501)
Anatomic site of cancer			
Hypopharynx	42 (16.5%) [a]	34 (13.8%)	76 (15.2%) [a]
Larynx	48 (18.8%) [a]	42 (17.1%)	90 (18.0%) [a]
Oral cavity	33 (12.9%)	38 (15.4%)	71 (14.2%)
Oropharynx	132 (51.8%)	131 (53.3%)	263 (52.5%)
Other	0 (0.0%)	1 (0.4%)	1 (0.2%)
Histopathological grade			
Well differentiated	31 (12.2%)	22 (8.9%)	53 (10.6%)
Moderately differentiated	97 (38.0%)	109 (44.3%)	206 (41.1%)
Poorly differentiated	72 (28.2%)	63 (25.6%)	135 (26.9%)
Undifferentiated	0 (0.0%)	2 (0.8%)	2 (0.4%)
Differentiation cannot be assessed	10 (3.9%)	11 (4.5%)	21 (4.2%)
Unknown	45 (17.6%)	38 (15.4%)	83 (16.6%)
Missing	0 (0.0%)	1 (0.4%)	1 (0.2%)
Reason for inoperability			
Technical unresectability	92 (36.1%)	84 (34.1%)	176 (35.1%)
Selection based on low surgical curability	78 (30.6%)	75 (30.5%)	153 (30.5%)
Organ preservation	85 (33.3%)	87 (35.4%)	172 (34.3%)
Clinical T stage			
T1	13 (5.1%)	9 (3.7%)	22 (4.4%)
T2	43 (16.9%)	56 (22.8%)	99 (19.8%)
T3	74 (29.0%)	88 (35.8%)	162 (32.3%)
T4	125 (49.0%)	92 (37.4%)	217 (43.3%)
TX	0 (0.0%)	1 (0.4%)	1 (0.2%)
Clinical N stage			
N0	42 (16.5%)	35 (14.2%)	77 (15.4%)
N1	53 (20.8%)	49 (19.9%)	102 (20.4%)
N2	128 (50.2%)	123 (50.0%)	251 (50.1%)
N3	32 (12.5%)	38 (15.4%)	70 (14.0%)
NX	0 (0.0%)	1 (0.4%)	1 (0.2%)
Time from 1st diagnosis to randomization (months)			
III	41 (16.1%)	46 (18.7%)	87 (17.4%)
IV	214 (83.9%)	199 (80.9%)	413 (82.4%)
Missing	0 (0.0%)	1 (0.4%)	1 (0.2%)
Time from 1st diagnosis to randomization (months)			
Median	0.9	0.9	0.9
Minimum	0.1	0.1	0.1
Maximum	32.5	9.7	32.5

ITT = intent to treat; TPF = docetaxel + cisplatin + 5-FU; PF = cisplatin + 5-FU, N = number of patients

[a] One patient was miscategorized in the database as having a primary tumor site of larynx, but the actual site was hypopharynx. This miscategorization is corrected in the text above this table, but not in this table.

Primary efficacy endpoint

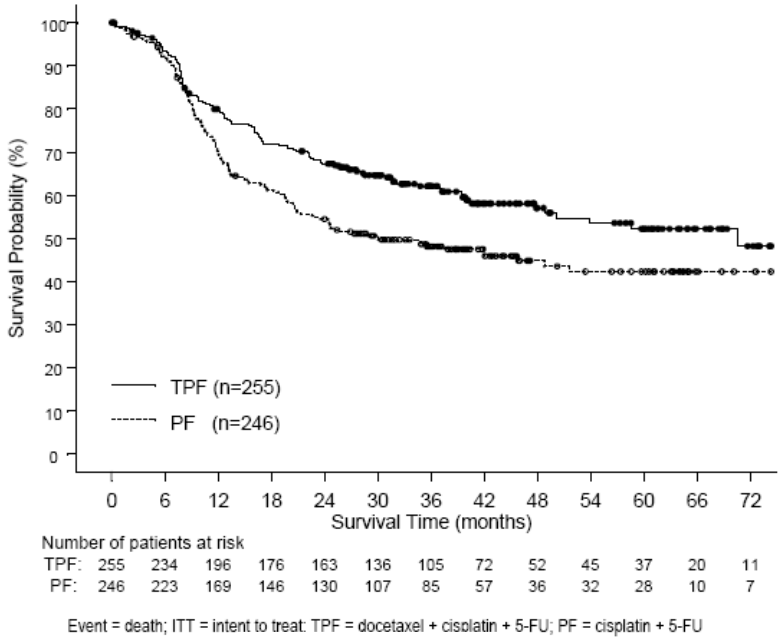
The primary endpoint was overall survival in the ITT population, using a log-rank test. OS was measured from the date of randomization to the date of death for any cause.
At the cut-off date, 234 of the 501 patients had died (46.7%): 40.8% in the TPF arm and 52.8% in the PF arm, as shown in table 4 and figure 2.

Table 4-Overall survival (ITT)

	RANDOMIZATION GROUP		
	TPF (N=255)	PF (N=246)	ALL (N=501)
Number of patients with			
Event	104 (40.8%)	130 (52.8%)	234 (46.7%)
Censored data	151 (59.2%)	116 (47.2%)	267 (53.3%)
Censoring reasons (Survival)			
Lost to follow-up	15 (5.9%)	14 (5.7%)	29 (5.8%)
Date of last contact before the cut-off date	7 (2.7%)	3 (1.2%)	10 (2.0%)
No event at cut-off date	129 (50.6%)	99 (40.2%)	228 (45.5%)

Cut-off date = 03DEC2005
ITT = intent to treat: TPF = docetaxel + cisplatin + 5-FU; PF = cisplatin + 5-FU; N = number of patients

Figure 2-Overall survival-Kaplan-Meier curve (ITT)



Event = death; ITT = intent to treat: TPF = docetaxel + cisplatin + 5-FU; PF = cisplatin + 5-FU

Table 5 summarizes the statistical data for overall survival in the ITT population.

	RANDOMIZATION GROUP	
	TPF (N=255)	PF (N=246)
Median overall survival (months) [95% CI]	70.6 [49.0 - NA]	30.1 [20.9 - 51.5]
Kaplan-Meier estimates for overall survival		
1-year estimate [95% CI]	80.0% [75.0 - 84.9]	69.9% [64.1 - 75.7]
2-year estimate [95% CI]	67.3% [61.5 - 73.2]	54.5% [48.2 - 60.8]
3-year estimate [95% CI]	62.1% [55.9 - 68.2]	48.1% [41.7 - 54.5]
Hazard ratio: TPF/PF [95% CI]	0.70 [0.54 - 0.90]	
Log-rank p value	0.0058	

ITT = intent to treat; TPF = docetaxel + cisplatin + 5-FU; PF = cisplatin + 5FU; CI = confidence interval; NA = not applicable; N = number of patients
Hazard ratio <1 favors TPF.

Survival estimated rate was also in favor of TPF regimen after 2 and 3 years: 67.3% TPF arm vs. 54.5% PF arm and 62.1% vs. 48.1%.

- Cox model

The potential effect of stratification factors of randomization (primary tumor site, N stage and center) have been investigated using a Cox proportional hazard model.
The treatment effect was statistically significant (p=0.0018) with a 34% risk reduction of mortality in the TPF arm compared to PF arm. Two factors of randomisation were statistically significant (p=0.009 for primary tumour site and p<0.0001 for the geographical area). The N stage wasn't statistically significant (p=0.0781). Similar results were obtained after analysis was performed on the stratification factors as recorded in the CRF after validation.

- Center effect

55 centers in six countries enrolled patients in the study. The number of centers by country ranged from 1 center to 42 centers. The number of patients by centre ranged from 1 patient to 73 patients. In the cox model, centers have been pooled by geographical area.
The consistency of OS across countries or centre size was examined and demonstrated a wide overlap of the 95% CI for the hazard ratio, indicating consistent results across the centres and the geographical area. The results of centres size (small/large) and geographical area were consistent with the overall results in favouring TPF.

- Subgroup analysis by primary tumor site

The consistency of OS across primary tumour sites was examined in the ITT population. It demonstrated a wide overlap of the 95% CI for the hazard ratio, indicating consistent results across the primary tumour site. A trend toward significance in favour of TPF (upper CI limits close to 1) was observed for patients with oropharynx and larynx primary tumour site (HR=0.70, 95% CI: 0.47-1.03, and HR=0.58, 95% CI: 0.32-1.04, respectively).

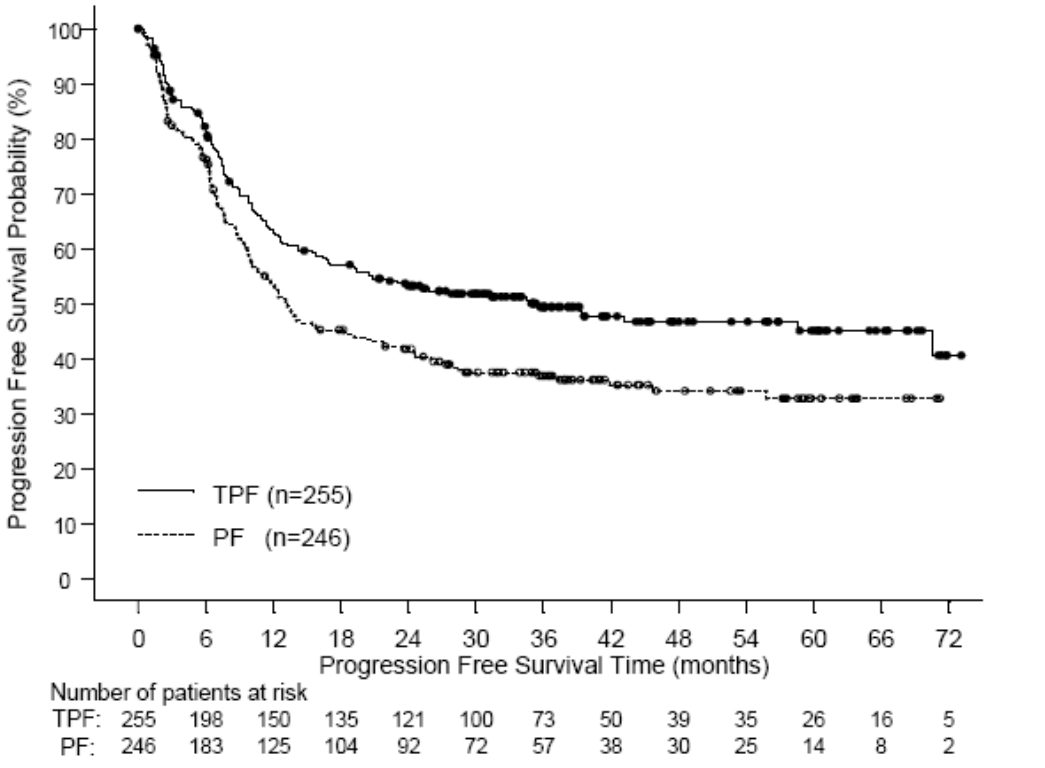
- Patient lost to follow-up

A sensitivity analysis was performed to evaluate patients lost to follow-up (TPF: 5.9%; PF: 5.7%) having had an event. TPF treatment was associated with a 28% (95% CI, 0.09 TO 0.44) risk reduction in mortality compared to PF (P=0.0067).

Secondary efficacy endpoint: Progression-free survival

PFS was calculated from the date of randomization to the date of progression or the date of death for any reasons. At the cut-off date, 125 patients (49%) in the TPF treatment group and 153 patients (62.2%) in the PF treatment group had developed a progression (37.6 % TPF vs. 47.2% PF) or are died (11.4% TPF vs. 15% PF).

Figure 3-Progression-free survival – Kaplan-Meier curve (ITT)



Event = progression of disease, death; ITT = intent to treat; TPF = docetaxel + cisplatin + 5-FU; PF = cisplatin + 5-FU

PFS was significantly higher in the TPF treatment group than in the PF treatment group. There was a 29% progression risk reduction for the TPF treatment group compared to the PF treatment group (HR=0.71, 95% CI: 0.56-0.90; p=0.004). Median PFS was 35.5 months in the TPF treatment group (95% CI: 19.3-NA) and 13.1 months in the PF treatment group (95% CI: 10.6-20.2), representing a 22-month improvement. Survival estimates at 2 years were 53.2% for the TPF treatment group compared to 41.7% for the PF treatment group.

Tumour assessments were to be performed in both treatment groups at the end of Cycles 2 and 3, 6 to 12 weeks after completion of chemoradiotherapy, and on follow-up visits until disease progression or death. Most tumour assessments were performed at the protocol-specified time points and were balanced between treatment groups. Overall, the progression endpoint was evaluated sooner in the TPF treatment group than in the PF treatment group. However, the positive treatment effect of TPF on PFS could not be attributed to tumour assessment timing.

Sensitivity analyses

When censoring for non-tumour related deaths, the difference between treatment groups showed a 31% progression risk reduction for the TPF treatment group compared to the PF treatment group (HR=0.69, 95% CI: 0.53-0.89; p=0.004).

When censoring for further therapies, the difference between treatment groups indicated a 33% progression risk reduction for the TPF treatment group compared to the PF treatment group (HR=0.67, 95% CI: 0.52-0.85; p=0.0013).

Other secondary efficacy endpoints

- Best overall response to induction chemotherapy is summarized in table 6.

Table 6- Best overall response to induction chemotherapy (ITT)

	RANDOMIZATION GROUP	
	TPF	**PF**
	(N=255)	**(N=246)**
Complete Response	42 (16.5%)	37 (15.0%)
Partial Response	141 (55.3%)	121 (49.2%)
No Change	30 (11.8%)	41 (16.7%)
Progression Disease	17 (6.7%)	24 (9.8%)
Not Evaluable	24 (9.4%)	23 (9.3%)
Missing	1 (0.4%)	0 (0.0%)
Overall RR (CR+PR) 95% CI	71.8% [65.8-77.2]	64.2% [57.9-70.2]
p value	0.070	
Complete RR (CR) 95% CI	16.5% [12.1-21.6]	15.0% [10.8-20.1]
p value	0.661	

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

- Best overall response after chemoradiotherapy is summarized in table 7.

Table 7-Clinical response at the end of chemoradiotherapy (ITT)

	RANDOMIZATION GROUP	
	TPF (N=202)	PF (N=184)
Complete Response	83 (41.1%)	65 (35.3%)
Partial Response	70 (34.7%)	70 (38.0%)
No Change	13 (6.4%)	9 (4.9%)
Progression Disease	20 (9.9%)	27 (14.7%)
Not Evaluable	16 (7.9%)	13 (7.1%)
Overall RR (CR+PR) 95% CI	75.7% [69.2-81.5]	73.4% [66.4-79.6]
p value	0.593	
Complete RR (CR) 95% CI	41.1% [34.2-48.2]	35.3% [28.4-42.7]
p value	0.245	

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

- Best overall response at the end of the study treatment

Table 8-Best overall response to induction chemotherapy and chemoradiotherapy (ITT)

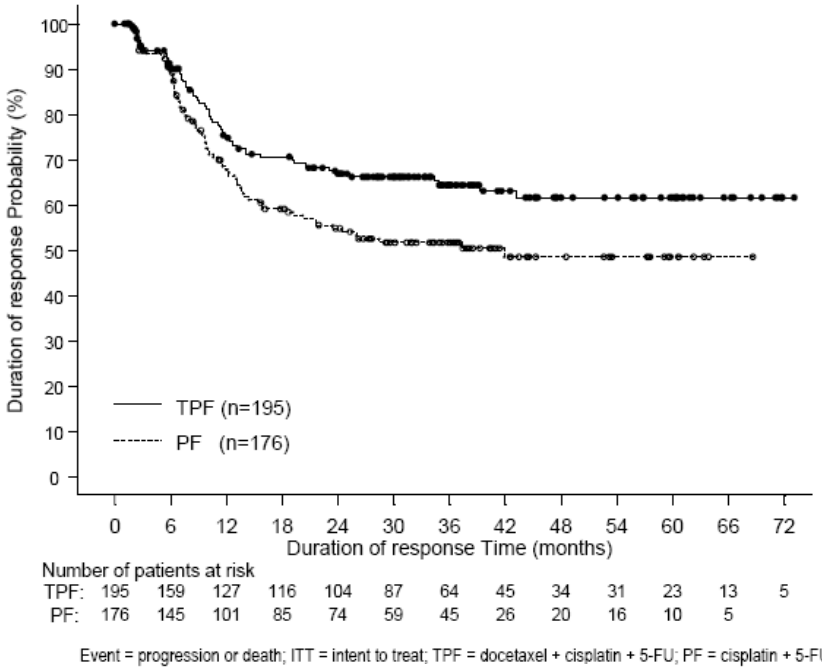
	RANDOMIZATION GROUP	
	TPF (N=255)	PF (N=246)
Complete Response	90 (35.3%)	69 (28.0%)
Partial Response	105 (41.2%)	107 (43.5%)
No Change	23 (9.0%)	30 (12.2%)
Progression Disease	15 (5.9%)	22 (8.9%)
Not Evaluable	21 (8.2%)	18 (7.3%)
Missing	1 (0.4%)	0 (0.0%)
Overall RR (CR+PR) 95% CI	76.5% [70.8-81.5]	71.5% [65.5-77.1]
p value	0.209	
Complete RR (CR) 95% CI	35.3% [29.4-41.5]	28.0% [22.5-34.1]
p value	0.082	

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

Duration of the response

Median duration of response was not reached in the TPF treatment group; it was 41.9 months (95% CI: 19.2-NA) in the PF treatment group. The difference between treatment groups was statistically significant, with HR=0.67 (95% CI: 0.48-0.93; p=0.018).

Figure 4-Duration of response – Kaplan-Meier curve (responders)



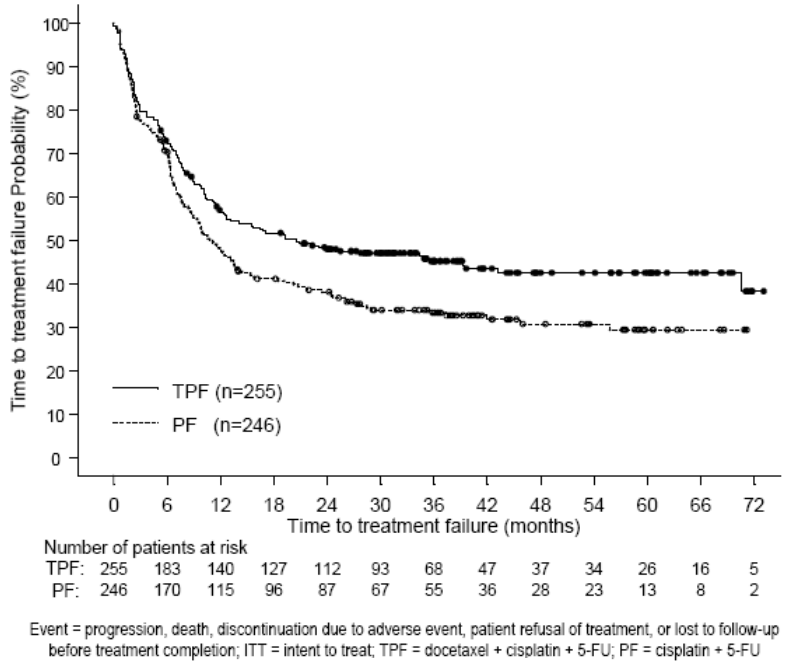
Event = progression or death; ITT = intent to treat; TPF = docetaxel + cisplatin + 5-FU; PF = cisplatin + 5-FU

Time to treatment failure

Observations of lost to follow-up after the end of treatment were censored. At the cut-off date, 60.7% of the ITT population had experienced a treatment failure, independent of treatment: Progressive disease was the main cause of an event (39.9%) in both treatment groups.

Median TTF was longer in the TPF treatment group (20.5 months; 95% CI: 12.6-39.4) than in the PF treatment group (10.8 months; 95% CI: 8.7-13.8). The difference between treatment groups was statistically significant with HR=0.74 (95% CI: 0.59-0.93; P=0.0102).

Figure 5-Time to treatment failure – Kaplan-Meier curve (ITT)



Event = progression, death, discontinuation due to adverse event, patient refusal of treatment, or lost to follow-up before treatment completion; ITT = intent to treat; TPF = docetaxel + cisplatin + 5-FU; PF = cisplatin + 5-FU

Analysis of efficacy by subgroup (gender, age and race)
Subgroup analyses were performed to assess the effects of gender, age and race on measures of efficacy. As shown in the description of the population the majority of patients were male, Caucasian and less than 65 years.

Quality of life and clinical benefit

Functional Assessment of Cancer Therapy Head and Neck (FACT-HN)

At least one evaluable quality of life assessment was obtained in 83.9% and 85.8% of TPF and PF patients, respectively. These percentages decreased with time from 96.8% at baseline to 30.5% at the end of treatment and over.

The analysis was made on the material from the 420 patients (209 in TPF arm and 211 in PF arm) who completed at least baseline assessment and one evaluable on-study assessment. No statistical difference was found between treatment groups (P=0.46). At baseline, the QLQ-H&N35 mean score was similar in the two treatment groups (24.1 in TPF, 24.2 in PF). The score improved at most by 2.4 points in the TPF treatment group and 1.7 points in the PF treatment group during the chemotherapy time windows. Similar conclusions applied to the Emotional Well Being score and the FACT-G score.

Performance Status Scale for Head and Neck (PSS-HN)

At baseline, almost all patients completed the PSS-HB assessment. The percentages decreased with time to approximately 60% at the end of treatment and over. Given the low compliance of the scale during follow-up, the mixed models applied on each subscale were limited to the first two time windows, corresponding to the induction chemotherapy treatment.
No statistically significant difference between treatment groups was found for the “Eating in public” and “Normalcy of diet” subscales (p=0.09 for both scales). In both treatment groups, the score did not vary clearly over time and was approximately 80.
The difference between treatment groups was significant for the “Understandability of speech” scale (p= 0.0196). However, when adjusting on multiplicity testing, the difference was borderline (p=0.06).

At baseline, the "Understandability of speech" means score was similar in the two treatment groups (89.1 in TPF, 89.8 in PF). The score in both treatment groups improved during treatment: 5.6 points in the TPF arm and 2.0 points in the PF arm during the chemotherapy time windows.

Pain intensity

It was evaluated with a visual analog scale, and it was associates with analgesic consumption. Overall, compliance over time of the pain intensity VAS was similar in the two treatment groups, with a significant decrease at the follow-up time points compared to end of chemotherapy in both treatment groups.
Given the low compliance of the scale during follow-up, the mixed models applied on each subscale were limited to the first two time windows, corresponding to the induction chemotherapy treatment. The difference between treatment groups were not statistically significant (p=0.14). Baseline intensity score was 25.6 in the TPF treatment group (n=209) versus 24.5 in the PF treatment group (n=201). In both treatment groups, pain intensity score was improved by at most 15.9 points in the TPF treatment group and 13.1 points in the PF treatment group during the chemotherapy time windows.
Most patients in both treatment groups (73.7% in TPF, 70.3% in PF) reported using analgesics at study entry (mainly of opioids). During induction chemotherapy, 81.6% of patients in the TPF treatment group and 83.7% in the PF treatment group received at least one analgesic, consisting mainly of opioids (about 65% in both treatment groups). However, the percentage of patients consuming analgesics during the induction chemotherapy treatment decreased from 70% to 60% in both treatment groups at the end of Cycle 3. During chemoradiotherapy, the percentage of patients with analgesics increased to 70% in the TPF treatment group and 66% in the PF treatment group.

Pharmacokinetic study
Pharmacokinetic studies were made for docetaxel, cisplatin and 5-FU. For analysis plasma sample were taken from 4 patients (3 in TPF treatment group and 1 in PF control group). Docetaxel and cisplatin concentrations were assessed in 3 patients and 5-FU concentration in 4 patients.

Discussion on Clinical Efficacy

Pharmacokinetics
Docetaxel pharmacokinetic parameters were calculated for 3 patients in the TPF treatment group, cisplatin parameters were calculated for 2 patients in the TPF treatment group and 1 patient in the PF treatment group, and 5-FU parameters were calculated for 3 patients in the TPF treatment group and 1 patient in the PF treatment group. Although data were limited, values for pharmacokinetic parameters of all 3 drugs were in the expected range.

Clinical efficacy
TAX 324 was a prospective, non-blinded, randomized, controlled, phase III trial comparing TPF (docetaxel, cisplatin, and 5-fluorouracil) with PF (cisplatin, and 5-fluorouracil) as induction regimen before chemoradiation for locally advanced squamous cell cancer of the head and neck. In the predominantly US-based multicenter phase III study, 538 patients with histologically or cytologically proven locally advanced SCCHN were included. The population of patients included those who are technically unresectable, those with low probability of surgical cure (<20% chance of cure), and those who could be resected but wanted to maintain function (organ preservation) each group comprising approximately one third of the patient population.

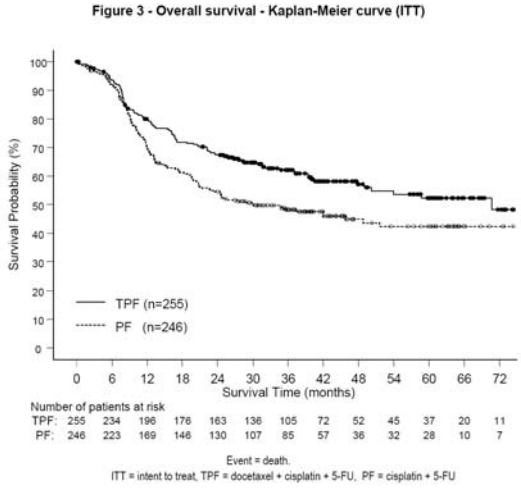
Patients were to receive 3 cycles of **induction chemotherapy** unless progression, unacceptable toxicity or patient refusal at the following dosing schedule, which was given every 3 weeks:
1 **TPF:** Docetaxel 75 mg/m² as 1-hour IV infusion followed by cisplatin 100 mg/m² as 30-min to 3-hour IV infusion on day 1. 5-FU followed as a continuous IV infusion at 1000 mg/m² per day on days 1-4 days.
2˜ **PF:** Cisplatin 100 mg/m² as 30-min to 3-hour IV infusion on day 1. 5-FU followed as a continuous IV infusion at 1000 mg/m² per day 1 for 5 days.

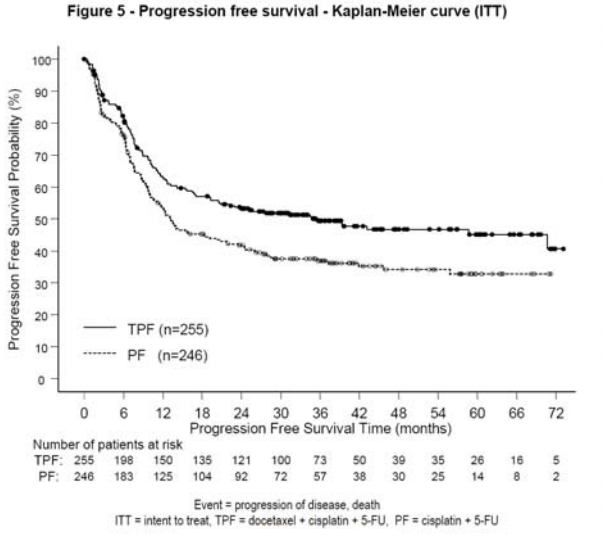
After the end of neoadjuvant chemotherapy, **locoregional therapy** with chemoradiation including carboplatin as a radiosensitizer had to be started within 3 to 8 weeks. **Radiation** was to be delivered using once daily fractionation (2 Gray [Gy] x 1/day, 5 days per week for 7 weeks). **Carboplatin** was given weekly as a 1-hour infusion for a maximum of 7 doses according to the radiation schedule. **Surgery** for resectable primary and/or nodal metastatic disease at the primary site and/or neck were allowed at any time following completion of chemoradiotherapy.

Patients were stratified for the participating centre, according to primary tumour site (oral cavity versus hypopharynx versus larynx) and stage (N0–1 vs. N2-3). From the baseline characteristics and tumour characteristics the two treatment groups are comparable. The vast majority of patients received chemotherapy and chemoradiotherapy as outlined in the protocol.

The results for the primary endpoint OS and for the secondary endpoints PFS and response rate are all in favour of treatment with TPF with HR= 0.70[0.54-0.9] for OS (Fig. 1) and HR=0.71[0.56-0.9] for PFS. The difference in median length of OS is 40.5 months, the difference in median length in PFS is 22.4 months, and the difference in overall response rate at the end of study treatment approximately 2.3%. Due to the high rate of censoring after 24 months and the median length of follow-up of 41.9 months, the survival estimates beyond the median follow-up time should be interpreted with caution (Table 1).

Fig. 1 Kaplan-Meier curves – overall survival and progression-free survival





The p-values of both log-rank tests were significant: p=0.0058 for OS and p=0.004 for PFS. The results for the overall response rate are only marginally significant after induction therapy (p=0.07)

and no longer significant at the end of study treatment (p=0.593). Duration of response was significantly longer in the subgroup of responders of the TFP group. Time to treatment failure was also significantly longer in the TPF arm.

Table 1 Summary statistics for overall survival

Table 46 - Summary statistics for overall survival (ITT)

	RANDOMIZATION GROUP	
	TPF (N=255)	PF (N=246)
Median overall survival (months) [95% CI]	70.6 [49.0 - NA]	30.1 [20.9 - 51.5]
Kaplan-Meier estimates for overall survival		
1-year estimate [95% CI]	80.0% [75.0 - 84.9]	69.9% [64.1 - 75.7]
2-year estimate [95% CI]	67.3% [61.5 - 73.2]	54.5% [48.2 - 60.8]
3-year estimate [95% CI]	62.1% [55.9 - 68.2]	48.1% [41.7 - 54.5]
Hazard ratio: TPF/PF [95% CI]	0.70 [0.54 - 0.90]	
Log-rank p value	0.0058	

ITT = intent to treat, TPF = docetaxel + cisplatin + 5-FU, PF = cisplatin + 5FU, CI = confidence interval,
NA = not applicable, N = number of patients
Hazard ratio <1 favors TPF.

Table 2 Summary statistics for progression free survival

Table 50 - Summary statistics for progression free survival (ITT)

	RANDOMIZATION GROUP	
	TPF (N=255)	PF (N=246)
Median PFS (months) [95% CI]	35.5 [19.3 - NA]	13.1 [10.6 - 20.2]
Kaplan-Meier estimates for PFS		
1-year estimate [95% CI]	63.0% [56.9 - 69.0]	53.3% [47.0 - 59.7]
2-year estimate [95% CI]	53.2% [46.9 - 59.5]	41.7% [35.4 - 48.0]
3-year estimate [95% CI]	49.4% [42.9 - 55.9]	36.8% [30.6 - 43.1]
Hazard ratio: TPF/PF [95% CI]	0.71 [0.56 - 0.90]	
Log-rank p value	0.004	

ITT = intent to treat, TPF = docetaxel + cisplatin + 5-FU, PF = cisplatin + 5-FU, C I= confidence interval,
PFS = progression free survival, NA = not applicable, N = number of patients
Hazard ratio <1 favors TPF.

Quality of Life (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 follow-up time-points. There were no statistically significant differences between the groups concerning QoL parameters neither at baseline nor during study treatment. Pain intensity improved during treatment in both groups indicating adequate pain management in both treatment groups.

Overall, the efficacy results of study TAX 324 are convincing in terms of clinically relevant and statistically significant decreased risk of death (OS) and of progression (PFS).

All provided post hoc analyses within the response document, further confirm the superiority of TPF vs. PF in various settings across the included population. The overall treatment plan with radio-chemotherapy after induction chemotherapy and surgery if considered medically appropriate reflects current clinical practice. Study TAX 324 confirms the benefit of induction treatment with TPF in patients with inoperable locally advanced head and neck cancer. Exploratory subgroup analyses with patients aiming at organ preservation also resulted in a survival benefit with the docetaxel containing triple drug induction as compared to the two drug regimen (cisplatin and 5-fluorouracil).

The induction chemotherapy comparator regimen is well recognised. At the time of the initiation of Study TAX 324, reference chemotherapy treatment in this neoadjuvant setting of SCCHN was cisplatin 100 mg/m^2 plus 5-fluorouracil 1000 mg/m^2. However, it is worth noting that the CRT regimen used in study TAX 324 must be considered as suboptimal. More intensive chemotherapy is usually used for a CRT based regimen (cisplatin 100mg/m^2). However, section 5.1 of the SPC adequately describes the design, treatment and outcome of study TAX 324, including a description of the CRT regimen used in the pivotal trial.

In the context of locally advanced head and neck cancer, it is important to highlight the difference between inoperable patients (in whom surgery is technically impossible or not indicated) and patients in whom surgical resection is not accepted. In the first setting, organ preservation is not an option and surgery is simply not feasible. In the second one, surgery is theoretically possible and could be the most efficient solution if the aim is prolongation of OS (there are no data contradicting this hypothesis).

The fact that organ preservation was not addressed in the TAX 324 study, is mentioned specifically in section 5.1 of the SPC in order to prevent the promotion of abstention from surgery in patients who are in principle operable. It is furthermore possible, that a trial comparing a chemotherapeutic regimen with a surgical approach is not feasible due to patient's preference. In this context, it is important to note that the results of the TAX 324 trial confirm that in both the overall patient population as well as in patients aiming at organ preservation and who are not operated, TPF is superior to PF.

Therefore, with reference to the wording of section 4.1 of the SPC, both the inclusion criteria of the TAX 324 study and the favourable results for the TPF group justify the deletion of the word "inoperable" from the current indication in head and neck cancer.

Clinical safety

Study TAX324

- **Patient exposure**

A total of 494 patients received study treatment in TAX324 and comprise the safety population, including 251 TPF-treated patients and 243 PF-treated patients. The safety analysis focused on the treated safety population.
The chemoradiotherapy safety population (CRSP) included 202 TPF patients and 184 PF patients.

Exposure to induction chemotherapy

In both treatment groups, the majority of patients received the protocol-specified 3 cycles of induction chemotherapy (84.1% of patients in the TPF treatment group and 81.9% of patients in the PF treatment group).
In the TPF treatment group, there were fewer patients with 1 or more cycle delays (29.1%) than in the PF treatment group (64.6%). Considering all patients, the most frequent reason for cycle delay was hematological toxicity, but only in the PF treatment group (44.4%, compared to 4.4% in the TPF treatment group).
Considering dose reduction, 21.9% of patients in the TPF treatment group and 25.9% of patients in the PF treatment group had at least 1 dose reduction. The most frequent reason for dose reduction in both treatment groups was non-hematological toxicities (TPF: 14.7%; PF: 19.8%).

Exposure to chemoradiotherapy

The majority of patients in both treatment groups of TAX324 received protocol-defined chemoradiotherapy (TPF 80.5%, PF 75.7%). In both treatment groups, the median duration of chemoradiotherapy was 7 weeks, and the median total dose of radiotherapy was 70.0 Gray. The median RDI of carboplatin during chemoradiotherapy was very high and similar across treatment groups.

- **Treatment-emergent Adverse events (TEAEs)**

Overview of TEAEs during chemotherapy

The percentages of patients who experienced at least 1 TEAE, both regardless of relationship to study treatment and possibly or probably related to study treatment, respectively, were 99.6% and 98.4% in the TPF treatment group and 99.2% and 97.1% in the PF treatment group. The frequency of Grade 4 events, regardless of relationship to study treatment, was 27.9% in the TPF treatment group and 24.7% in the PF treatment group. The frequency of drug-related Grade 4 events was 24.3% in the TPF treatment group and 20.6% in the PF treatment group.

Overview of number of patients with TEAEs during induction chemotherapy (SP)

	TREATMENT RECEIVED	
	TPF [a] (N=251)	PF (N=243)
Number of patients on chemotherapy		
- With at least one TEAE	250 (99.6%)	241 (99.2%)
- With at least one G3/4 TEAE	163 (64.9%)	151 (62.1%)
- With at least one G4 TEAE	70 (27.9%)	60 (24.7%)
- With at least one TEAE related	247 (98.4%)	236 (97.1%)
- With at least one G3/4 TEAE related	137 (54.6%)	118 (48.6%)
- With at least one G4 TEAE related	61 (24.3%)	50 (20.6%)

TEAEs regardless of relationship

The incidences by patient of TEAEs -regardless of relationship- were similar in the 2 treatment groups for most NCIC CTG categories (National Cancer Institute of Canada Clinical Trials Group), with only the skin category having a >10% difference in any grade TEAE between the 2 treatment groups (TPF: 78.5%; PF: 63.8%).

During chemotherapy the 5 most frequent NCIC CTG terms for TEAEs (all grades, regardless of relationship to study treatment, in either treatment group) occurring in more than 50% of patients were nausea (TPF: 76.5%; PF: 79.8%), alopecia (TPF: 67.7%; PF: 43.6%), stomatitis (TPF: 65.7%; PF: 67.5%), lethargy (TPF: 61.4%; PF: 55.6%), and vomiting (TPF: 56.2%; PF: 62.6%).

TEAEs related to treatment

The 2 treatment groups were similar for most NCIC CTG categories, related to study treatment, with only the system "skin" having a >10% difference in incidence by patient for any grade TEAE between the 2 treatment groups (TPF: 72.5%; PF: 57.2%). Related TEAE categories of gastrointestinal and flu-like symptoms had Grade 3/4 TEAEs with a frequency of >10% in either treatment group (gastrointestinal: TPF: 43.0%; PF: 38.3%; flu-like symptoms: TPF: 7.6%; PF: 12.8%). These same 2 categories (gastrointestinal and flu-like symptoms) were the only categories with >3% difference in Grade 3/4 TEAEs between the 2 treatment groups.

Patients with TEAEs during induction chemotherapy, by NCIC CTG category, related to study treatment (SP)

NCIC CTG classification	TREATMENT RECEIVED			
	TPF [a] (N=251)		PF (N=243)	
Number of patients without TEAE	4 (1.6%)		7 (2.9%)	
Number of patients with TEAE	247 (98.4%)		236 (97.1%)	
	Grade 3/4	ALL	Grade 3/4	ALL
Gastrointestinal	108 (43.0%)	233 (92.8%)	93 (38.3%)	226 (93.0%)
Skin	13 (5.2%)	182 (72.5%)	7 (2.9%)	139 (57.2%)
Flu-like symptoms	19 (7.6%)	170 (67.7%)	31 (12.8%)	141 (58.0%)
Neurologic	16 (6.4%)	108 (43.0%)	13 (5.3%)	124 (51.0%)
Cardiovascular	13 (5.2%)	50 (19.9%)	18 (7.4%)	38 (15.6%)
Infection	9 (3.6%)	33 (13.1%)	10 (4.1%)	38 (15.6%)
Pulmonary	6 (2.4%)	31 (12.4%)	4 (1.6%)	30 (12.3%)
Weight		28 (11.2%)	5 (2.1%)	32 (13.2%)
Hypersensitivity	5 (2.0%)	25 (10.0%)		7 (2.9%)
Genitourinary	4 (1.6%)	17 (6.8%)	5 (2.1%)	12 (4.9%)
Cancer related symptoms	3 (1.2%)	9 (3.6%)		3 (1.2%)

NCIC CTG classification	TREATMENT RECEIVED			
	TPF [a] (N=251)		PF (N=243)	
Number of patients without TEAE	4 (1.6%)		7 (2.9%)	
Number of patients with TEAE	247 (98.4%)		236 (97.1%)	
	Grade 3/4	ALL	Grade 3/4	ALL
Ocular		9 (3.6%)		7 (2.9%)
Endocrine		4 (1.6%)	1 (0.4%)	3 (1.2%)
Blood bone marrow		2 (0.8%)	1 (0.4%)	2 (0.8%)
Dentition		2 (0.8%)		2 (0.8%)
Other	1 (0.4%)	1 (0.4%)		
Coagulation			1 (0.4%)	1 (0.4%)
Hepatic			1 (0.4%)	1 (0.4%)

The 2 treatment groups were similar for most NCIC CTG terms related to study treatment (all grades). The most frequent related TEAEs occurring in more than 50% of patients were nausea (TPF: 75.7%; PF: 78.2%), alopecia (TPF: 67.7%; PF: 43.2%), stomatitis (TPF: 64.5%; PF: 67.1%), lethargy (TPF: 58.6%; PF: 51.0%), and vomiting (TPF: 56.2%; PF: 60.9%). Only alopecia had a >10% difference between the 2 treatment groups. TEAE terms of nausea and stomatitis had Grade 3/4 TEAEs with a frequency of >10% in either treatment group (nausea: TPF: 13.9%; PF: 13.6%; stomatitis: TPF: 20.7%; PF: 27.2%, anorexia: TPF: 12.0%; PF: 11.1%, esophagitis/dysphagia/odynophagia: TPF: 12.0%; PF: 7..4%). Of the 4 Grade 3/4 related TEAE terms with >3% difference in incidence between the 2 treatment groups, 2 were more frequent in the TPF treatment group: diarrhea (TPF: 6.8%; PF: 3.3%) and esophagitis/dysphagia/odynophagia (TPF: 12.0%; PF: 7.4%) and 2 were more frequent in the PF treatment group: stomatitis (TPF: 20.7%; PF: 27.2%) and lethargy (TPF: 4.0%; PF: 9.9%).
The following related TEAEs occurred in <5% of patients but were considered to be clinically meaningful given the known safety profiles of docetaxel, cisplatin, or 5-FU: dysrhythmias (TPF: 3.2%; PF: 2.1%), myocardial ischemia (TPF: 0.8%; PF: 0.4%), gastrointestinal bleeding (TPF: 2.0%; PF: 1.2%), hay fever (TPF: 2.4%; PF: 1.6%), conjunctivitis/keratitis (TPF: 0.8%; PF: 0.0%), and tearing (TPF: 1.6%; PF: 1.6%). Of these, Grade 3/4 related TEAEs were seen for dysrhythmias (TPF: 2.0%; PF: 1.6%), myocardial ischemia (TPF: 0.8%; PF: 0.4%), gastrointestinal bleeding (TPF: 0.4%; PF: 0.4%), and hay fever (TPF: 0.4%; PF: 0.0%).

TEAEs during chemoradiotherapy

The percentages of patients who experienced at least 1 TEAE, both regardless of relationship to study treatment and possibly or probably related to study treatment, were similar in the 2 treatment groups. The 2 treatment groups were similar for most NCIC CTG categories related to study treatment, with no NCIC CTG category having a >10% difference between treatment groups. There were 2 Grade 3/4 TEAE categories having a >3% difference in incidence between the 2 treatment groups: gastrointestinal (TPF: 48.5%; PF: 53.3%), which was more frequent in the PF treatment group, and skin (TPF: 12.9%; PF: 9.8%), which was more frequent in the TPF treatment group.
The 2 treatment groups were similar for most NCIC CTG terms (all grades) related to study treatment. The most frequent related TEAEs occurring in more than 50% of patients were stomatitis (TPF: 81.7%; PF: 84.8%), esophagitis/dysphagia/odynophagia (TPF: 63.4%; PF: 60.3%), and mouth/nose dryness (TPF: 53.5%; PF: 51.6%). The terms with Grade 3/4 related TEAEs occurring in >10% of patients in both treatment groups were stomatitis (TPF: 36.1%; PF: 37.5%) and esophagitis/dysphagia/odynophagia (TPF: 21.8%; PF: 21.2%). Anorexia (TPF: 8.4%; PF: 13.0%) was the only Grade 3/4 TEAE term with >3% difference in incidence between the 2 treatment groups.

- **Serious adverse events**

Serious TEAEs during chemotherapy

The frequencies of patients who experienced at least 1 serious TEAE of any grade, regardless of relationship to study treatment, was 43.4% in the TPF treatment group and 36.2% in the PF treatment group. 92 (36.7%) patients in the TPF group experienced serious related adverse events and 72 (29.6%) in the PF group.

Overview of number of patients with serious TEAEs (SP)

	TREATMENT RECEIVED	
	TPF [a] (N=251)	PF (N=243)
Number of patients on chemotherapy		
- With at least one serious TEAE	109 (43.4%)	88 (36.2%)
- With at least one serious G3/4 TEAE	86 (34.3%)	72 (29.6%)
- With at least one serious G4 TEAE	52 (20.7%)	47 (19.3%)
- With at least one serious TEAE related	92 (36.7%)	72 (29.6%)
- With at least one serious G3/4 TEAE related	69 (27.5%)	58 (23.9%)
- With at least one serious G4 TEAE related	43 (17.1%)	38 (15.6%)

Serious TEAEs regardless of relationship

The 2 treatment groups were similar for most NCIC CTG terms for serious TEAEs during induction chemotherapy by patient (all grades, regardless of relationship). There was a difference of ≥3% in the incidence between the treatment groups in fever in the absence of infection (TPF: 15.5%; PF: 9.1%) and granulocytes (TPF: 6.8%; PF: 2.1%).

Serious TEAEs related to treatment

The 2 treatment groups were similar for most NCIC CTG terms for related serious TEAEs during induction chemotherapy by patient (all grades).

The most frequent (≥5% in either group) terms were fever in the absence of infection (TPF: 15.1%; PF: 8.6%), granulocytes (TPF: 6.8%; PF: 2.1%), stomatitis (TPF: 6.0%; PF: 8.6%), and vomiting (TPF: 5.6%; PF: 4.5%).

Patients with related serious TEAEs during induction chemotherapy, by NCIC CTG term, of all grades, in ≥2 patients (SP)

NCIC CTG TERM	TREATMENT RECEIVED	
	TPF [a] (N=251)	PF (N=243)
Number of patients without serious TEAE	159 (63.3%)	171 (70.4%)
Number of patients with serious TEAE	92 (36.7%)	72 (29.6%)
Fever in absence of infection	38 (15.1%)	21 (8.6%)
Granulocytes	17 (6.8%)	5 (2.1%)
Stomatitis	15 (6.0%)	21 (8.6%)
Vomiting	14 (5.6%)	11 (4.5%)
Esophagitis/dysphagia/odynophagia	12 (4.8%)	8 (3.3%)
Creatinine	11 (4.4%)	9 (3.7%)
Infection	11 (4.4%)	9 (3.7%)
Diarrhea	9 (3.6%)	7 (2.9%)
Nausea	9 (3.6%)	12 (4.9%)
Anorexia	7 (2.8%)	9 (3.7%)
Hypokalemia	5 (2.0%)	1 (0.4%)
Dysrhythmias	4 (1.6%)	2 (0.8%)
Hyponatremia	3 (1.2%)	2 (0.8%)
Hypotension	2 (0.8%)	3 (1.2%)
Lethargy		4 (1.6%)
Platelets		3 (1.2%)

Serious TEAEs during chemoradiotherapy

The frequencies of patients who experienced at least 1 serious TEAE of any grade, regardless of relationship to study treatment, was 18.8% in the TPF treatment group and 25.5% in the PF treatment group. 25 (12.4%) patients in the TPF treatment group experienced serious related TEAEs against 31 (16.8%) in the PF treatment group.

There was a difference of ≥3% in incidence between treatment groups for stomatitis (TPF: 3.0%; PF: 6.0%) and esophagitis/dysphagia/ odynophagia (TPF: 2.0%; PF: 5.4%).

- **Deaths on study**

Of the 494 treated patients, 103 (41.0%) TPF-treated patients and 130 (53.5%) PF-treated patients died. Progression of disease was the main cause of death in both treatment groups (TPF: 28.7%; PF: 40.7%) and occurred more than 30 days after the last study treatment in all but one (PF-treated) patient. Toxic death was observed in 2 TPF-treated patients, one occurring 154 days after the last study treatment, and in 4 PF-treated patients, one occurring 57 days after the last study treatment. The "other" category consisted mostly of adverse events not related to study treatment, and in 8 patients (5 in TPF, 3 in PF), death of unknown cause.

Summary of deaths (SP)

	TREATMENT RECEIVED	
	TPF [a] (N=251)	PF (N=243)
Total deaths	103 (41.0%)	130 (53.5%)
- Progression of disease	72 (28.7%)	99 (40.7%)
- Toxicity	2 (0.8%)	4 (1.6%)
- Other	29 (11.6%)	27 (11.1%)
Within 30 days of last study treatment	4 (1.6%)	12 (4.9%)
- Progression of disease	0 (0.0%)	1 (0.4%)
- Toxicity	1 (0.4%)	3 (1.2%)
- Other	3 (1.2%)	8 (3.3%)
More than 30 days after last study treatment	99 (39.4%)	118 (48.6%)
- Progression of disease	72 (28.7%)	98 (40.3%)
- Toxicity	1 (0.4%)	1 (0.4%)
- Other	26 (10.4%)	19 (7.8%)

Both with and without chemoradiotherapy, the most common reason for death was progressive disease: 38.8% and 55.9% for TPF- and PF-treated patients, respectively, who did not receive chemoradiotherapy, and 26.2% and 35.9% for TPF- and PF-treated patients, respectively, who received chemoradiotherapy.

Deaths within 30 days of last study treatment

Deaths within 30 days of last study treatment from non-malignant cause (i.e., due to "toxicity" or "other") were more frequent in the PF treatment group (12 patients, 4.9%) than in the TPF treatment group (4 patients, 1.6%).

A quarter of the deaths in both treatment groups (TPF: 1 of 4 deaths; PF: 3 of 12 deaths) were reported as toxic deaths by the investigator.

Infection was the most common AE leading to a non-malignant cause of death within 30 days of the last study treatment, with 1 patient in the TPF treatment group and 3 patients in the PF treatment group who had infection-associated deaths.

Deaths more than 30 days after last study treatment

Overall, 217 patients (43.9%) died at least 30 days after the last study treatment: 99 in the TPF treatment group (39.4%) and 118 in the PF treatment group (48.6%).

Of these 217 deaths, 11 were due to AEs (with onset prior to 30 days after the last study treatment, or considered related): 6 in the TPF treatment group and 5 in the PF treatment group. 9/11 were assessed as not related to the study treatment.

- **Withdrawal due to adverse events**

Discontinuation of study treatment due to AEs occurred in 10.2% of TPF patients and in 8.5% of PF patients, with no particular AE leading to discontinuation.

- **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 12.4% of patients in the TPF group and 9.5% in the PF group.
Leukopenia of any grade occurred in 92.8% of patients in the TPF group and 79.8% 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 (54.2%) than in the PF group (23.5%), with the majority of these being Grade 3 leukopenia.
Neutropenia of any grade was more frequent among patients in the TPF group (94.8%) than in the PF group (84.2%). Grade 3/4 neutropenia was also more frequent in the TPF group (83.5%) than in the PF group (56.0%), regardless the use of G-CSF.
Prophylactic G-CSF was given to a total of 68 evaluable patients (13.8%), limiting assessment of benefit.
The percentage of patients with any grade **thrombocytopenia** was similar in the TPF treatment group (27.5%) and in the PF treatment group (30.9%). Grade 3/4 thrombocytopenia was more frequent in the PF group (10.7%) than in the TPF group (4.0%).

Serum chemistry:
Abnormalities of creatinine clearance occurred with similar frequency in the two treatment groups (all grades: TPF: 20.9%; PF: 20.2%).
The parameters of any grade reported with a difference >10% were hypomagnesemia (TPF: 61.4%; PF: 42.8%) and hypocalcemia (TPF: 36.7%; PF: 24.9%), both of which were more frequent in the TPF treatment group than in the PF treatment group.
Grade 3/4 abnormalities reported with a difference >3% were hypomagnesemia (TPF: 6.3%; PF: 2.8%) and hypocalcemia (TPF: 12.7%; PF: 6.6%).
Hypomagnesemia
Grade 3/4 hypomagnesemia was reported in 14 (6.3%) patients in the TPF treatment group versus 6 (2.8%) patients in the PF treatment group. Hypomagnesemia has been reported in patients treated with platinum compounds.
Hypocalcemia
Grade 3/4 hypocalcemia was reported in 31 (12.7%) patients in the TPF treatment group versus 15 (6.6%) patients in the PF treatment group. In the cancer patient population, hypocalcemia is frequently seen in association with hypoalbuminemia (for example, in presence of malnutrition). Because calcium is bound to albumin, low albumin levels result in artifactually lower laboratory calcium values. Furthermore, magnesium levels, often low in poor nutritional settings, could also contribute to decreased calcium levels. Albumin levels were reported in 21 patients in the TPF treatment group and 8 patients in the PF treatment group; among these, decreased albumin levels (lower than 3.5 g/dL) were found in 11 patients in the TPF treatment group and 3 patients in the PF treatment group; all these 14 patients (with known decreased albumin levels) exhibited a Grade 3/4 hypocalcemia (uncorrected for albumin levels). Upon correction, only 3 of the 14 patients demonstrated Grade 3/4 hypocalcemia. Correction of calcium levels based on corresponding albumin levels resulted in fewer cases of Grade 3/4 hypocalcemia in both treatment groups.

- **Specific Safety Issues**

Neutropenic infection and febrile neutropenia
Prophylactic antibiotics were used primarily in the TPF treatment group. A total of 244 patients from the TPF treatment group (97.2%) and 68 patients from the PF treatment group (28.0%) received primary prophylaxis with antibiotics.

Secondary infection prophylaxis with G-CSF was required in all subsequent cycles after the first episode of febrile neutropenia or documented Grade 3/4 neutropenia with documented infection. In addition, if there was a second episode, the patient was to remain on ciprofloxacin and G-CSF and, additionally, during subsequent cycles, the docetaxel dose was to be reduced from 75 mg/m^2 to 60 mg/m^2. The table below presents the number of patients experiencing neutropenic infection and febrile neutropenia during induction chemotherapy, regardless of prophylactic G-CSF. Most patients

were evaluable for febrile neutropenia and neutropenic infection. In correlation with the increased incidence of neutropenia Grade 4 in the TPF treatment group (63.3% compared to 28.2% in the PF group) there was a higher number of patients with febrile neutropenia (TPF: 12.1%; PF: 6.6%) or neutropenic infection (TPF: 11.7%; PF: 8.3%). All cases of febrile neutropenia and the majority of those for neutropenic infection (TPF: 55.2%; PF: 80.0%) were considered to be related to study treatment. There were no deaths due to febrile neutropenia. One patient in the TPF treatment group and 1 patient in the PF treatment group died due to neutropenic infection.

Neutropenic infection and febrile neutropenia during induction chemotherapy - number of patients (SP)

	TREATMENT RECEIVED			
	TPF [a] (N=251)		PF (N=243)	
Evaluable patients for assessing neutropenic infection [b]	248	(98.8%)	241	(99.2%)
Neutropenic infection (any relationship) [c]	29	(11.7%)	20	(8.3%)
Neutropenic infection (related infection) [c]	16	(6.5%)	16	(6.6%)
Deaths due to neutropenic infection	1	(0.4%)	1	(0.4%)
Evaluable patients for assessing febrile neutropenia [b]	248	(98.8%)	241	(99.2%)
Febrile Neutropenia (any relationship) [d]	30	(12.1%)	16	(6.6%)
Febrile Neutropenia (related fever) [d]	30	(12.1%)	16	(6.6%)
Deaths due to febrile neutropenia	0	(0.0%)	0	(0.0%)

Fluid retention
All patients in the TPF treatment group were to receive corticosteroids to prevent a hypersensitivity reaction and also to reduce or delay fluid retention. There were more patients with fluid retention in the TPF treatment group (13.1%) than in the PF treatment group (7.0%). The most frequent associated symptom was edema only (12.0% TPF, 5.8% PF).

Neurologic events
Baseline neurologic signs and symptoms were present in 67.5% of TPF patients and 69.5% of PF patients. During the induction chemotherapy period, neurologic events related to chemotherapy were experienced by 32.7% of patients in the TPF treatment group compared to 35.8% of patients in the PF treatment group. The events were primarily Grade 1 and 2. The Grade 3/4 events had a similar incidence in the both treatment groups (TPF: 4.8%; PF: 4.5%), and the most frequent were hearing disorders. The majority of events were altered hearing (TPF: 12.7%; PF: 18.5%), sensory (TPF: 13.9%; PF: 14.4%), or motor (TPF: 8.8%; PF: 10.3%).

- **Risk Management Plan**

Due to the ample experience with docetaxel as such, the safety profiles observed in the clinical trials TAX323 and TAX324 and the information provided in the SPC, ongoing pharmacovigilance practice and procedures are considered adequate to continuously monitor the safety profile of docetaxel. Therefore, no Risk Management Plan was considered necessary as part of the current application and no additional risk minimisation measures beyond the Product Information are required.

Discussion on Clinical Safety

Docetaxel has been licensed in Europe as well as in many other countries worldwide for treatment of different malignancies, mostly in combination therapy. Its safety profile is well known and is described in the SPC. Study TAX 324 has not shown a different safety profile of docetaxel as compared to study TAX 323 and previous studies.

The Treatment Emergent Adverse Events (TEAE) that were more commonly reported with TPF compared with PF can mostly be attributed 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 (6.2 % vs. 11.6 %). It is encouraging that the experimental treatment was associated with fewer deaths within 30 days of study treatment and that as well fewer deaths due to infections were observed with the three-drug combination compared to the two-drug combination. The routine antibiotic prophylaxis in the TPF group may account to this difference.

The adverse drug reactions - as observed in study TAX 324 - have been displayed in a table in the SPC. A similar table has previously been included in the SPC for study TAX 323. This approach is considered acceptable and the information adequate about adverse drug reactions during use of docetaxel in combination with cisplatin and 5-fluorouracil for treatment of SCCHN. No additional risk minimisation measures beyond the Product Information are required.

Benefit-risk assessment

Patients with 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 in the treatment of locally advanced SCCHN shows evidence that integrating chemotherapy into the treatment plan of locally advanced disease might lead to improved survival of patients with unresectable disease.

Docetaxel Winthrop in combination with cisplatin and 5-fluorouracil was approved for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck based on the TAX 323 study. TAX 323 assessed the benefit of induction chemotherapy (TPF vs. PF) followed by conventional radiotherapy.

The results of the phase III study TAX 324, comparing induction treatment with Docetaxel plus Cisplatin plus 5-Fluorouracil (TPF) to treatment with Cisplatin plus 5-Fluorouracil (PF), both arms were followed by chemoradiotherapy (CRT) have now been provided as part of the present variation application. Based on these data, the MAH has applied to broaden the head and neck cancer indication in section 4.1 of the SPC. The proposed wording is:
"Docetaxel Winthrop (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."

Study TAX 324 investigated induction chemotherapy (TPF vs. PF) followed by concomitant radio-chemotherapy (carboplatin AUC 1.5 weekly and 2 Gy per day, 5 days per week for 7 weeks, for a total dose of 70-72 Gy).
Patients were randomised to receive either:
-Test group docetaxel (75 mg/m2 D1) associated with cisplatin (100 mg/m2 D1) and 5-FU (1000 mg/m2/D1-4) (TPF, Q 3 weeks x 3 cycles)
- Control group: cisplatin (100 mg/m2 D1) and 5-FU (1000 mg/m 2/ D1-5) (PF, Q 3 weeks x 3 cycles).
Randomization was stratified upon 3 factors: the primary tumour site (oral cavity vs. oropharynx vs. hypopharynx vs. larynx), the N stage (N0-N1 vs. N2-N3) and the centre.

The population of patients included those who are technically unresectable, those with low probability of surgical cure (<20% chance of cure), and those who could be resected but wanted to maintain function (organ preservation). Each group comprised of approximately one third of the patient population overall. The study population was well balanced based on demographic and clinical criteria: the majority of patients were men (83.6%) with good performance status (WHO PS 0 or 1), and the median age was 56 years (33 to 82). The most frequent tumour site was oropharynx (52.5%) and the most frequent TNM stage, in both groups, was T4/N2.

The primary efficacy analysis was a comparison of Overall Survival (OS) adjusted for prognostic factors in the ITT population at the end of the study using a Cox proportional hazards model.

Induction chemotherapy with docetaxel (TPF regimen) was associated with a 30% of risk reduction in mortality (HR =0.70; 95% CI 0.54-0.9; p=0.0058).

The secondary analysis supported the conclusions of the primary analysis:
- Progression Free survival (PFS) was higher in the TPF arm; there was a 29% progression risk reduction (HR=0.71; 95% CI 0.56-0.90; p=0.004).
- Best overall response rate to study treatment (induction chemotherapy and chemoradiotherapy) was 76.5% in the TPF group and 71.5% in the PF group.
- Duration of response: not reached in TPF arm, 41.9 months in the PF arm.
- Time to treatment failure was in favour of the TPF treatment group (20.5 months vs. 10.8 months).

No difference between groups was observed in the Quality of Life and Clinical benefit assessment.

Overall, the efficacy results of study TAX 324 are convincing in terms of clinically relevant and statistically significant decreased risk of death (OS) and of progression (PFS).

All provided post hoc analyses within the response document, further confirm the superiority of TPF vs. PF in various settings across the included population. The overall treatment plan with radio-chemotherapy after induction chemotherapy and surgery if considered medically appropriate reflects current clinical practice. Study TAX 324 confirms the benefit of induction treatment with TPF in patients with inoperable locally advanced head and neck cancer. Exploratory subgroup analyses with patients aiming at organ preservation also resulted in a survival benefit with the docetaxel containing triple drug induction as compared to the two drug regimen (cisplatin and 5-fluorouracil).

The induction chemotherapy comparator regimen is well recognised. At the time of the initiation of Study TAX 324, reference chemotherapy treatment in this neoadjuvant setting of SCCHN was cisplatin 100 mg/m^2 plus 5-fluorouracil 1000 mg/m^2. However, it is worth noting that the CRT regimen used in study TAX 324 must be considered as suboptimal. More intensive chemotherapy is usually used for a CRT based regimen (cisplatin 100mg/m^2). However, section 5.1 of the SPC adequately describes the design, treatment and outcome of study TAX 324, including a description of the CRT regimen used in the pivotal trial.

In the context of locally advanced head and neck cancer, it is important to highlight the difference between inoperable patients (in whom surgery is technically impossible or not indicated) and patients in whom surgical resection is not accepted. In the first setting, organ preservation is not an option and surgery is simply not feasible. In the second one, surgery is theoretically possible and could be the most efficient solution if the aim is prolongation of OS (there are no data contradicting this hypothesis).

However, the fact that organ preservation was not addressed in the TAX 324 study, is mentioned specifically in section 5.1 of the SPC in order to prevent the promotion of abstention from surgery in patients who are in principle operable. It is furthermore possible, that a trial comparing a chemotherapeutic regimen with a surgical approach may not be feasible due to patient's preference. In this context, it is important to note that the results of the TAX 324 trial confirm that in both the overall patient population as well as in patients aiming at organ preservation and who are not operated, TPF is superior to PF.

Therefore, with reference to the wording of section 4.1 of the SPC, both the inclusion criteria of the TAX 324 study and the favourable results for the TPF group justify the deletion of the word "inoperable" from the current indication in head and neck cancer. The revised indication reads: *"Docetaxel Winthrop 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."*

Further changes refer to SPC sections 4.2 posology and method of administration, 4.8 undesirable effects, 5.1 Pharmacodynamic properties. The Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to make minor editorial changes to the SPC and to update the annexes in line with the latest QRD template, which is acceptable.

Currently, the value of induction chemotherapy in SCCHN remains controversial. TAX 324, by design, solely addressed the question of the efficacy and safety of one induction chemotherapy regimen compared to another and succeeded in demonstrating a favourable outcome within a heterogenous population of patients, both operable and inoperable. Overall, however, the value of the triple induction regimen within the multimodal treatment of head and neck cancer (specifically with respect to functional conservation) remains to be determined in other therapy optimising clinical trials.

From the safety viewpoint, cutaneous toxicities are reported more frequently in the TPF arm compared to the PF arm. However, despite serious toxicities, discontinuation or toxic deaths were rarely reported.
TAX 324 presented toxicities generally tolerable and manageable. Study TAX 324 did not show a different safety profile of docetaxel as compared to study TAX 323 and previous studies. All in all, the safety profile is in accordance with the expected safety profile of docetaxel, cisplatin and 5-FU.

IV. CONCLUSION

- On 18 October 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.