Taxotere in Palliative Therapy (TInPaT):

A Pilot Study of Taxotere (Docetaxel), Cisplatin and 5FU (TPF) in the Palliative Treatment of Squamous Cell Carcinoma of the Head and Neck
End of Study Report
Author - Dr Caroline Brammer - Chief Investigator

Name of test drug/investigational product

Taxotere 75mg/m2 D1 , Cisplatin 75mg/m2 D1 and 5FU 750mg/m2 D1-4

Indication studied

Palliative chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck Patients must have had disease that was considered unsuitable for radical treatment with either surgery or radiotherapy. Either or both forms of treatment may have been used previously in patients who had progressive disease. Recurrence must have been outside of a previously irradiated area if radiotherapy had been completed within 6 months of study entry

Study Description

This non commercial pilot study investigated Taxotere (Docetaxel) 75mg/m2 over 1 hr i.v. Day 1 plus Cisplatin i.v.75mg/m2 Day 1 over 2hrs plus 5FU 750 mg/m2 i.v. over 24hrs Day 1-4. in adult patients with recurrent or metastatic carcinoma of the head and neck.

Name of the sponsor

The Royal Wolverhampton Hospitals NHS Trust

REC reference: 07/H1211/148
Protocol Number: 2006-002-0201-ONC
EudraCT number :2006-005816-29
Development phase of study :Phase 2

Study initiation date = 30/04/2009
First patient enrolled = 28/05/2009
Date of early study termination: Study terminated 13th January 2011
Chief Investigator:

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The Study was carried out following the principles of GCP.

Monitored by: Research and Development (RWHT)

Report Date: 19/12/2011

SYNOPSIS

This non commercial single arm, unblinded, non-randomised pilot study investigated Taxotere (Docetaxel) 75mg/m2 over 1 hr i.v. Day 1 plus Cisplatin i.v.75mg/m2 Day 1 over 2hrs plus 5FU 750 mg/m2 i.v. over 24hrs Day 1-4.

Patients were eligible for inclusion if the following criteria were met:

a) Aged over 18 and less than or equal to 70 at study entry
b) Histologically proven squamous carcinoma the head and neck, excluding carcinoma of the nasopharynx .
c) Patients must have disease that is considered unsuitable for radical treatment with either surgery or radiotherapy. Either or both forms of treatment may have been used previously in patients who have progressive disease but measurable disease recurrence must be present outside of a previously irradiated area if radiotherapy was completed within 6 months of randomisation.
d) Patients must be considered fit for chemotherapy.
e) ECOG performance status of 0,1 or 2.(appendix 4).
f) Able and willing to give written informed consent and to comply with the protocol for the duration of treatment and follow up.
g) Expected survival greater than 3 months from entry into study
h) Adequate renal function.
    a. Calculated Cockroft/Gault GFR ≥ 60ml/min or
    b. EDTA GFR ≥ 50ml/min
i) Measurable Disease. Defined as 1 measurable lesion where the longest diameter is ≥ 20mm on conventional CT or ≥ 10mm on spiral CT or MRI. or direct clinical measurement ≥ 10mm

The following patients were excluded

a) Women who are lactating or pregnant.
b) Patients who have received previous chemotherapy for recurrent malignant disease or any cytotoxic chemotherapy within 6 months prior to study entry.
c) Patients who have received radiotherapy within 6 weeks or if they have ongoing acute radiotherapy toxicity.
d) A history of nervous or psychiatric disorder that would preclude informed consent or compliance with oral drug intake or treatment
e) A history of previous malignancy within the previous 5 years except successfully treated basal cell cancer of skin or carcinoma in situ of cervix.
f) Patients with the following laboratory values
    1. Hb<10g/dl that cannot be corrected by blood transfusion.
    2. Neutrophil count<1.5x 109/L
    3. Platelets<100x109/L
    4. Serum bilirubin >1.5xULN
    5. ALT and/or AST>2.5xULN
    6. Alkaline phosphatase>2.5xULN
g) Patients with uncontrolled infection.
h) Patients with a history of severe hypersensitivity reactions to Taxotere (Docetaxel) .

The primary objective of the study to determine the response rate (CR plus PR) and tolerability of Taxotere (Docetaxel) 75mg/m2 over 1 hr i.v. Day 1 plus Cisplatin i.v 75mg/m2 Day 1 over 2hrs plus 5FU 750 mg/m2 i.v. over 24hrs Day 1-4 (TPF) for the palliative treatment of squamous cell carcinoma of the head and neck.After the first 3 patients were entered it was apparent that the toxicity of the regime was too high as all 3 patients required as dose reduction according to the protocol after the first cycle. An amendment reducing the dose of the chemotherapy to Taxotere (Docetaxel) 60mg/m2 over 1 hr i.v. Day 1 plus Cisplatin i.v 60mg/m2 Day 1 over 2hrs plus 5FU 600 mg/m2 i.v. over 24hrs Day 1-4 was submitted and a further 4 patients were recruited. Toxicity remained high, the study was suspended and a data monitoring committee convened to determine whether the study should continue (to allow active participation of the collaborating centres) or whether the study should close on the grounds of futility and toxicity. The study was therefore closed after 7 patients were recruited. The study was therefore only carried out on one site by the chief investigator and was not rolled out to other centres.

All patients entered receiving 2 or more cycles of chemotherapy were considered evaluable for response and all patients entered in the study were considered evaluable for toxicity.

All patients experienced grade 3 or 4 toxicity during the course of their treatment . The tumour response as determined by the Data Monitoring Committee (DMC) is detailed in table 1.
All patients recruited into the study were performance status 0 or 1 at study entry. Five males and 2 females were recruited. Median age at study entry was 63 years, range 51 – 65 years.
The results of the study are shown in the tables below.

Table 1 : Patient Details

	Age	Sex	Site	TNM Stage At study entry	Recurrent and/or Metastatic disease	Initial Dose TPF mg/m2	Dose reduction required	No. of Cycles	reason for stopping therapy	Tumour Response.	OS Weeks.
1	65	m	oro	TxN0M1	metastatic	75/75/750.	y after cycle1	6	completed treatment	PR PFS=18 weeks	48
2	60	m	hypo	T4N0	locally recurrent within previous XRT field	75/75/750	y after cycle1	2	progressive disease	PD	8
3*	56	f	oro hypo.	T4N2cM 1. T4N2cM 1	metastatic	75/75/750	y after cycle1	6	completed treatment	PR PFS=6 weeks	20
4	66	m	oro	T4N2M1	locally recurrent within previous XRT field and metastatic	60/60/600	n/a	1	Life threatening toxicity	n/a	15
5	65y	f	oro	T4N0M0	locally recurrent within previous XRT field	60/60/600	n/a	1	Life threatening toxicity	n/a	29
6	51y	m	oro	TxN3M0	loco regional recurrence outside radiotherapy field	60/60/600	n	6	completed treatment	PR PFS =9 weeks	34
7	63	m	oro	T4N2cM 1	metastatic	60/60/600 600 5FU	y after cycle1	2	withdrawn from study**	n/a	n/a

* two primary sites at diagnosis ** withdrawn when diagnosis of metastatic disease uncertain after cycle 2 (mediastinal nodes considered reactive not metastatic) , oro= oropharynx, hypo= hypopharynx, PFS = progression free survival, OS =overall survival

Table 2 Toxicity-Taxotere 75mg/m2 Day 1, Cisplatin 75mg/m2 Day 1 and 5FU 750mg/m2 Day 1-4

Toxicity	Number of patients suffering toxicity - all grades N=3	Number of patients suffering toxicity grade 3 or 4 N=3
Nausea	2	2
Mucositis	2	1
Vomiting	2	1
Diarrhoea	2	2
Fatigue	2	2
Constipation	1	0
Neutropenia	1	1
Anaemia	2	0
Dehydration	1	1
Renal	1	0

Table 3 Toxicity-Taxotere 60mg/m2 Day 1, Cisplatin 60mg/m2 Day 1 and 5FU 600mg/m2 Day 1-4

Toxicity	Number of patients suffering toxicity – all grade N=7	Number of patients suffering toxicity grade 3 or 4 N=7
Alopecia	7	0
Mucositis	4	2
Nausea	6	2
Vomiting	4	3
Diarrhoea	5	2
Fatigue	7	4
Constipation	1	0
Infection	3	3
Neutropenia	3	3
Anaemia	6	2
Thrombocytopenia	1	0
Dehydration	5	4
Renal	1	1
Hyperuraemia	1	1
Pericarditis	1	0
Hepatic dysfunction	1	0

6 out of 7 patients were admitted with conditions that were definitely or probably related to study medications. There were 5 admissions definitely related to study medications, 2 of which with a serious adverse event which was labelled as life threatening with a further 2 labelled as severe. 3 admissions were thought to be probably related to study medications 1 of which was labelled as life threatening, 1 moderate severity and 1 mild.
3 patients out of 4 who could be assessed for response had a partial response. Progression free survival however was short. (6, 9 and 18 weeks). 2 out of the 3 patients achieving a partial response were chemo-naïve.

TPF chemotherapy (Taxotere 60mg/m2 Day1. Cisplatin 60mg/m2 Day 1, 5FU 600mg/m2 Days 1-4) is considered too toxic for further study in patients with recurrent or metastatic SCCH+N despite prophylactic lenograstim and prophylactic antibiotic therapy. It is postulated that pre-treatment nutritional compromise secondary to the effects of tumours affects tolerability of this regime. TPF (Taxotere 60mg/m2 Day1. Cisplatin 60mg/m2 Day 1, 5FU 600mg/m2 Days 1-4) chemotherapy is not suitable for further investigation in this patient population.

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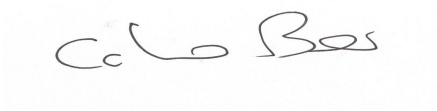
List of Abbreviations and Definition of Terms

Abbreviation	Definition
1. AE	Adverse Event
2. b.d.	twice a day
3. CR	Complete Response
4. CRF	Case Report Form
5. D1	Day 1of chemotherapy cycle
6. D1-4	Days 1-4 of chemotherapy cycle
7. DMC	Data Monitoring Committee
8. ECOG	Eastern Cooperative Oncology Group
9. EDTA	ethylenediaminetetraacetic acid
10. f	Female
11. F.R.C.R.	Fellow of Royal College of Radiologists
12. G-CSF	Granulocycte - Colony Stimulating Factor
13. GFR	Glomerular Filtration Rate
14. i.v.	Intravenous
15. m	Male
16. N	Number of
17. NCIC CTC	National Cancer Institute of Canada Common Toxicity Criteria
18. OS	Overall Survival
19. PD	Progressive Disease
20. PFS	Progression Free Survival
21. PR	Partial Response
22. R+D	Research and Development
23. REC	Regional Ethics Committee
24. RWHT	Royal Wolverhampton Hospitals Trust
25. SAE	Serious Adverse Event
26. SCCH+N	Squamous Cell Carcinoma of Head and Neck
27. TInPaT	Taxotere in PalliativeTherap y
28. t.d.s.	three times a day
29. TNM	Tumour, Nodes, Metastasis
30. TPF	Taxotere, Cisplatin and 5FU
31. ULN	Upper Limit Normal
32. XRT	Radiotherapy
33. **5HT3**	5-hydroxytryptamine 3 receptor

Author of Report:
Dr Caroline Brammer, Chief Investigator

Chief Investigator Acknowledgement:

I have read this report and confirm to the best of my knowledge it accurately describes the conduct and results of the study



Signed: Date:…13//01/2012…
Dr Caroline Brammer, Chief Investigator

Data Monitoring Committee:

Dr Andrew Hartly F.R.C.R. - Consultant Oncologist Queen Elizabeth Hospital, Birmingham - Chair
Dr Paul Sangera F.R.C.R, - Consultant Oncologist Queen Elizabeth Hospital,
Dr Sanjay Vydianath F.R.C.R. - Consultant Radiologist - New Cross Hospital Wolverhampton

Ethics
The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Patients were consented prior to any study procedures being undertaken specifically for the study.
All study documents and amendments were reviewed and approved by an Ethics Committee.

The Trial was reviewed by the Coventry and Warwickshire Local Research Ethics Committee. Lewes House, George Elliot Hospital NHS Trust, College Street Nuneton. Warwickshire CV10 7DJ.

Introduction
Cisplatin 100mg/m2, Day 1 and 5FU 1000mg/m2, days 1-2 for a maximum of 6 cycles has been the gold standard regime for palliation of locally recurrent or metastatic squamous cell carcinoma of the head and neck for many years but there was no documented survival benefit from this approach and treatment has been given purely for palliation of symptoms. The median survival following the development of recurrent or metastatic disease is approximately 6 months, with a 1 year survival of 20%. Taxotere (Docetaxel) was shown itself to be active in head and neck cancer and in neoadjuvant studies an overall survival benefit has been demonstrated. Addition of Taxotere (Docetaxel) to a combination of Cisplatin and 5FU as neoadjuvant therapy improved median survival from 14.5 months to 18.6 months in patients with unresectable squamous cell carcinoma of the head and neck treated by radical radiotherapy(excluding nasopharynx, nasal and paranasal cavities) . In this study the response rate for TPF was significantly greater than for cisplatin and 5FU alone, 67.9% vs 53.6% respectively (p=0.007)[8]. An improvement in response rate and overall median survival following the use of Taxanes in the recurrent or metastatic setting was suggested by a number of phase 2 studies[9,10,11]. This study was designed to assess the tolerability of TPF in patients with recurrent of metastatic squamous cell carcinoma of the head and neck.

Study objectives
Primary Objectives

To determine the response rate (CR plus PR) and tolerability of Taxotere (Docetaxel) Day 1 plus Cisplatin Day 1 over 2hrs plus 5FU Day 1-4 (TPF) every 21 days for a maximum of 6 cycles for the palliative treatment of squamous cell carcinoma of the head and neck.

Secondary Objectives

To assess the effect of TPF therapy on Quality of Life in this population
To assess the toxicity profile in this population.
To assess time to progression and survival status.

Study design

This was a phase 2 open label, single arm pilot study with no randomisation. This study design was chosen as a pilot study to ensure the safety of this regimen in this patient population before proceeding to a phase 3 study Initially 14 patients were to be registered. The trial was then to be suspended to further recruitment until data had been reviewed by an Independent Data Monitoring Committee (D.M.C.). If there was ≤1 response (PR or CR) then the study will have stopped. If were 2 or more toxic deaths attributable to chemotherapy amongst the initial 14 patients recruited to study, the study will have closed. If > 1 CR or PR had been seen, then a further 11 patients would have been recruited (Gehan stage 2 design). The Independent Data Monitoring Committee was to have confirmed the response status of the first 14 patients entered in to the study and would have given authorization for the trial to continue if the above criteria had been met.

All patients had their first cycle of chemotherapy within 14 days after consent and registration,. It was planned for 6 cycles to be given on a 21 day regime.

While there had been no patient deaths due to toxicity, 2 patients had the chemotherapy suspended after the first cycle due to life threatening toxicity. The DMC was therefore convened early to review the trial status and issued a recommendation to terminate the study on the grounds of toxicity and futility.

Selection of the study population

Inclusion cirteria

a) Aged over 18 and less than or equal to 70 at study entry

b) Histologically proven squamous carcinoma the head and neck, excluding carcinoma of the nasopharynx .

c) Patients must have disease that is considered unsuitable for radical treatment with either surgery or radiotherapy. Either or both forms of treatment may have been used previously in patients who have progressive disease but measurable disease recurrence must be present outside of a previously irradiated area if radiotherapy was completed within 6 months of randomisation.

d) Patients must be considered fit for chemotherapy.

e) ECOG performance status of 0, 1 or 2

f) Able and willing to give written informed consent and to comply with the protocol for the duration of treatment and follow up.

g) Expected survival greater than 3 months from entry into study

h) Adequate renal function.

   a. Calculated Cockroft/Gault GFR ≥ 60ml/min or
   b. EDTA GFR ≥ 50ml/min

i) Measurable Disease. Defined as 1 measurable lesion where the longest diameter is ≥ 20mm on conventional CT or ≥ 10mm on spiral CT or MRI. or direct clinical measurement ≥ 10mm

While the inclusion criteria included patients of performance status 2 all patients actually recruited in to the study were of performance status 0 or 1 as the chief investigator felt that it would be safer to ensure safety in the patients

of better performance status in the first few patients before widening the study to performance status 2 patients at the trial centre. Only when the regimen was to be shown to be safe in PS 0-2 patients would there have been plans to open the trial at the collaborating centres

Exclusion criteria

a) Women who are lactating or pregnant.

b) Patients who have received previous chemotherapy for recurrent malignant disease or any cytotoxic chemotherapy within 6 months prior to study entry.

c) Patients who have received radiotherapy within 6 weeks or if they have ongoing acute radiotherapy toxicity.

d) A history of nervous or psychiatric disorder that would preclude informed consent or compliance with oral drug intake or treatment

e) A history of previous malignancy within the previous 5 years except successfully treated basal cell cancer of skin or carcinoma in situ of cervix.

f) Patients with the following laboratory values

1. Hb<10g/dl that cannot be corrected by blood transfusion.
2. Neutrophil count<1.5x 109/L
3. Platelets<100x109/L
4. Serum bilirubin >1.5xULN
5. ALT and/or AST>2.5xULN
6. Alkaline phosphatase>2.5xULN

g) Patients with uncontrolled infection.

h) Patients with a history of severe hypersensitivity reactions to Taxotere (Docetaxel) .

Patient who had received chemotherapy within 6 months of study entry were excluded as these patients have a poor prognosis and generally have chemotherapy resistant disease. Taxotere is known to cause neutropenia and uncontrolled infection or pre - existing cytopenias would have put patients at significant risk of life threatening sepsis. Taxotere undergoes hepatic elimination therefore pre treatment hepatic dysfunction would increase the risk of toxicity.

Treatments administered

Single Arm Study:

The initial doses for the study (Taxotere 75mg/m^2 day 1, Cisplatin 75mg/m^2 day 1 and 5FU 750mg/m^2 day 1-4 were chosen as these were the doses of TPF used in tax 323 and Tax 324 which were the randomised 3 studies showing a survival benefit for patients with locally advanced head and neck cancer given neoadjuvant chemotherapy prior to radical radiotherapy or chemoradiotherapy with carboplatin. An amendment for the 20% dose reduction was sought after it was apparent that doses appeared too high, as the first 3 patients entered into the study had all suffered significant toxicity.

Day 1

Taxotere (Docetaxel) 75 -60 mg/m2 over 1 hr i.v.

N. Saline 1 lire over 2 hr

Manitol 20% 100mls over 15minutes

Cisplatin i.v.75-60mg/m2 Day 1 over 2hrs

N.Saline 1 litre over 2 hr plus Mg SO4 1g

plus

Day 2-5

5FU 750-600mg/m2 i.v. over 24hrs (may be given as an outpatient via Hickman line and syringe driver)

Plus Augmentin 625mg t.d.s. Days 7-16or Ciprofloxacin 500mg b.d. days 7-16

Plus G-CSF (Granocyte,Lenograstim) days 4-11

Delivered on a 21 day cycle

Maximum of 6 cycles

The first 3 patients in the study received their first treatment the 75mg/m^2 dose level and the final 4 at the 60mg/m^2 (Taxotere and Cisplatin), 750 reduced to 600mg/ m^2 for 5FU.

Drug Supply

The Taxotere for the study was supplied by Aventis from trial stock. The Cisplatin and 5FU was supplied from general stock the pharmacy department at New Cross Hospital Wolverhampton

Drug Preparation

Cisplatin and 5FU was reconstituted and labelled by the pharmacy department at New Cross Hospital Wolverhampton using regular stock. The Taxotere for use in the study was batched and labelled by Aventis for use the trial only and reconstituted at New Cross Hospital Pharmacy.

Supportive Medications

Antiemetics

A 5HT3 antagonist and dexamethasone combination should have been given as the participating centres policy for highly emetogenic regimes.

A combination of Emend, 5HT3 antagonist and dexamethasone may also be used.

Dexamethasone

Dexamethasone 8mg twice a day for 3 days should have been prescribed to commence 24 hours before delivery of Taxotere to prevent allergic reaction to Taxotere

Toxicity was graded using NCIC Common Toxicity Criteria version 3 and dose modification made for subsequent cycles.

Patients were instructed to take antiemetics as the regular practice for the participating centre. The choice of the antiemetic regime was that of the participation centre so compliance was not measured.

Patients were either taught to self administer G-CSF or a district nurse was arranged to administer the injection according to the choice of the patient. Compliance was not formally assessed.

No drug interactions between trial medications and supportive medications were expected.

Chemotherapy Dose Scheduling Modifications

Treatment Modifications During Chemotherapy

Heamatological

For patients whose nadir of platelet count during the previous course of therapy was <25000 cells/mm^3, or in patients who experienced febrile neutropenia the doses of cytotoxic drugs for the next cycle were reduced by 20%

(80% of starting dose). If there was a further febrile neutropenic event or platelet nadir of <25000 cells/mm^3 in the next cycle of TPF the Taxotere was to be discontinued.

Stomatitis and Diarrhoea

Cisplatin starting dose was to be maintained.

Toxicity NCIC Grade*	During a course of Therapy	Dose adjustment-Taxotere (Docetaxel) and 5FU only for next cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance 2nd appearance 3rd appearance 4th appearance	Interrupted until resolved to grade 0-1 Interrupted until resolved to grade 0-1 Interrupted until resolved to grade 0-1 Discontinue permanently	100% 80% 50%
Grade 3		
1st appearance 2nd appearance 3rd appearance	Interrupted until resolved to grade 0-1 Interrupted until resolved to grade 0-1 Discontinued permanently	80% 50%
Grade 4	Discontinued permanently	

Other

Toxicity NCIC Grade*	During a course of Therapy	Dose adjustment-all Drugs for next cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance 2nd appearance 3rd appearance 4th appearance	Interrupted until resolved to grade 0-1 Interrupted until resolved to grade 0-1 Interrupted until resolved to grade 0-1 Discontinued permanently	100% 80% 50%
Grade 3		
1st appearance 2nd appearance 3rd appearance	Interrupted until resolved to grade 0-1 Interrupted until resolved to grade 0-1 Discontinued permanently	80% 50%
Grade 4	Discontinued permanently	

Treatment Compliance

As the investigational products were intravenous, compliance was 100% as supported by the clinical staff within the hospital. Records of treatment are detailed on patient charts and notes as per standard hospital practice. Supportive drugs such as prophylactic antibiotics were supplied to the patient following chemotherapy. G-CSF was delivered by the patient's district nurse if the patient was unable or unwilling to inject themselves.

The delivery of GCSF and antibiotics compliance was informally assessed by asking the patients at the next clinic visit. Compliance was not formally assessed.

Efficacy and safety variables

Efficacy was initially determined by the chief investigator following clinical examination and review of the radiology reports. Patients were examined at every 3 weeks during treatment and tumour response measured by the most appropriate measure after cycle 3 and 6. Radiological response was subsequently verified by the data monitoring committee. For all 7 patients participating in the study the most appropriate manner of measuring the tumour was CT scan.
Toxicity was assessed by the chief investigator following each cycle of chemotherapy and graded as per National Cancer Institute Common Toxicity Criteria version 3. (NCI CTC v 3)

All efficacy and safety assessments were standard for giving chemotherapy to this set of patients. All patients were assessed within 3 days prior to each chemotherapy cycle.

Data Quality Assurance

At the start of the study, the monitoring of the trial was sub-contracted to the GMCRN where the monitoring of this study was performed erratically. Handover of Monitor was transferred back to the Trust following the R&D appointment of a trained Monitor. From 29 Sept 2010 the monitoring process was then planned and visits schedules were put into place until the end of study

Adverse events
Adverse events were identified by questioning the patient prior to each chemotherapy cycle. Expected events were recorded on the CRF as toxicities of treatment and graded as the NCI CTC version 3. Some serious events were identified when medical staff managing the patient contacted the chief investigators clinical team when the patient was admitted to hospital although the majority of unscheduled hospital admissions were identified at the scheduled patient review within 3 days of each chemotherapy cycle.

Statistics
As this was a small pilot phase 2 study. No formal statistics other than median progression free survival and median overall survival were planned. As only 7 patients were recruited to the study this was not applicable.

Protocol Deviations

One patient (final patient recruited in to the study) Tin 7 was withdrawn following the second cycle of chemotherapy as it was judged as likely that the assumed metastatic lymphadenopathy was reactive due to a discordant response to treatment between the primary site and the mediastinal lymph nodes. The patient was therefore judged to have potentially curable disease and therefore went on to receive radical chemoradiotherapy.

Tin 4 and Tin 5 received Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2 as a first dose of chemotherapy at the discretion of the chief investigator due to toxicity and patient safety concerns prior to the final approval of the amendment to reduce doses of chemotherapy to that level. This was not considered a serious breach as the

amendment had already been proposed. Both of these patient had life threatening toxicity despite the lower doses of chemotherapy being prescribed.

All patients were recruited by the eligibility criteria and radiological assessments conducted at the correct timepoints for the study up to when they were withdrawn and the study terminated early.

An amendment was submitted for quality of life assessments to provide a time window for quality of life questionnaire completion in the follow up phase rather than a specific time point as a specific time point proved impossible to strictly comply to.

Trial results

All patients experienced grade 3 or 4 toxicity during the course of their treatment . The tumour response as determined by the (DMC) is detailed in table 1.
All patients recruited into the study were performance status 0 or 1 at study entry. Five males and 2 females were recruited. Median age at study entry was 63 years, range 51 – 65 years.
The results of the study are shown in the tables below.

Table 1 : Patient Details

	Age	Sex	Site	Stage At study entry	Recurrent and/or Metastatic disease	Initial Dose TPF mg/m2	Dose reduction required	No. of Cycles	reason for stopping therapy	Tumour Response.	OS Weeks.
1	65	m	oro	TxN0M1	metastatic	75/75/750.	y after cycle1	6	completed treatment	PR PFS=18 weeks	48
2	60	m	hypo	T4N0	locally recurrent within previous XRT field	75/75/750	y after cycle1	2	progressive disease	PD	8
3*	56	f	oro hypo.	T4N2cM1. T4N2cM1	metastatic	75/75/750	y after cycle1	6	completed treatment	PR PFS=6 weeks	20
4	66	m	oro	T4N2M1	locally recurrent within previous XRT field and metastatic	60/60/600	n/a	1	Life threatening toxicity	n/a	15
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6	51y	m	oro	TxN3M0	loco regional recurrence outside radiotherapy field	60/60/600	n	6	completed treatment	PR PFS =9 weeks	34
7	63	m	oro	T4N2cM1	metastatic	60/60/600 600 5FU	y after cycle1	2	withdrawn from study**	n/a	n/a

* two primary sites at diagnosis ** withdrawn when diagnosis of metastatic disease uncertain after cycle 2 (mediastinal nodes considered reactive not metastatic) , oro= oropharynx, hypo= hypopharynx, PFS = progression free survival, OS =overall survival

Table 2 Toxicity-Taxotere 75mg/m2 Day 1, Cisplatin 75mg/m2 Day 1 and 5FU 750mg/m2 Day 1-4

Toxicity	Number of patients suffering toxicity - all grades	Number of patients suffering toxicity grade 3 or 4

	N=3	N=3
Nausea	2	2
Mucositis	2	1
Vomiting	2	1
Diarrhoea	2	2
Fatigue	2	2
Constipation	1	0
Neutropenia	1	1
Anaemia	2	0
Dehydration	1	1
Renal	1	0

Table 3 Toxicity-Taxotere 60mg/m2 Day 1, Cisplatin 60mg/m2 Day 1 and 5FU 600mg/m2 Day 1-4

Toxicity	Number of patients suffering toxicity – all grade N=7	Number of patients suffering toxicity grade 3 or 4 N=7
Alopecia	7	0
Mucositis	4	2
Nausea	6	2
Vomiting	4	3
Diarrhoea	5	2
Fatigue	7	4
Constipation	1	0
Infection	3	3
Neutropenia	3	3
Anaemia	6	2
Thrombocytopenia	1	0
Dehydration	5	4
Renal	1	1
Hyperuraemia	1	1
Pericarditis	1	0
Hepatic dysfunction	1	0

6 out of 7 patients were admitted with conditions that were definitely or probably related to study medications. There were 5 admissions definitely related to study medications, 2 of which with a serious adverse event which was labelled as life threatening with a further 2 labelled as severe. 3 admissions were thought to be probably related to study medications 1 of which was labelled as life threatening, 1 moderate severity and 1 mild.

3 patients out of 4 who could be assessed for response had a partial response. Progression free survival however was short. (6, 9 and 18 weeks). 2 out of the 3 patients achieving a partial response were chemo-naïve.

Toxicity recorded by individual patient and consequent actions

All toxicities grades as NCI CTC v 6.

Patient 1 = TIN 1
Cycle 1 Taxotere 75mg/m2, Cisplatin 75mg/m2, 5FU 750mg/m2
Grade 3 or 4 toxicity

Nausea	grade 3
Vomiting	grade 3
Diarrhoea	grade 3
Fatigue	grade 3 (in bed 2 weeks)

Grade 2 toxicity
Mucositis grade 2
Action dose reduction to Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2

Cycle 2 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity
Fatigue grade 3 (still in bed 2 weeks after chemotherapy)
Grade 2 toxicity
Nausea grade 2
Vomiting grade 2
Diarrhoea grade 2
Action continue same dose

Cycle 3 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity
Fatigue grade 3 (in bed 2 weeks)
Grade 2 toxicity
Alopecia grade 2
Action continue same dose

Cycle 4 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 2 toxicity
Alopecia grade 2
Action continue same dose

Cycle 5 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity
Nausea grade 3
Vomiting grade 3
Grade 2 toxicity
Diarrhoea grade 2
Alopecia grade 2
Action Dose reduction Taxotere 48mg/m2, Cisplatin 48mg/m2, 5FU 480mg/m2

Cycle 6 Taxotere 48mg/m2, Cisplatin 48mg/m2, 5FU 480mg/m2
Grade 3 or 4 toxicity
Nil
Grade 2 toxicity
Nausea grade 3
Diarrhoea grade 2
Alopecia grade 2

COMPLETED TREATMENT
OVERALL RESPONSE PARTIAL RESPONSE
TIME TO PROGESSION 10/11/09 (last treatment) to 27/05/10 (bone mets) = 28 weeks
Overall Survival 10/11/09 to 29/09/10 = 48 weeks

Patient 2 =TIN 2
Cycle 1 Taxotere 75mg/m2, Cisplatin 75mg/m2, 5FU 750mg/m2
Grade 3 or 4 toxicity
Diarrhoea grade 3
Fatigue grade 3
Neutropenia grade 4
Grade 2 toxicity
anaemia grade 2
Action dose reduction to Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2

Cycle 2 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity
Vomiting grade 3 (still in bed 2 weeks after chemotherapy)
Neutropenia grade 4
anaemia grade 4
Fatigue grade 3
Infection grade 3
Grade 2 toxicity
Nausea grade 2
Diarrhoea grade 2
Action Treatment discontinued

WITHDRAWN AFTER 2 CYCLES
OVERALL RESPONSE DISEASE PROGRESSION
TIME TO PROGESSION N/A
Overall Survival 15/09/09 to 5/11/09 = 8 weeks

Patient 3 = TIN 3
Cycle 1 Taxotere 75mg/m2, Cisplatin 75mg/m2, 5FU 750mg/m2
Grade 3 or 4 toxicity
Nausea grade 3
Mucositis grade 3
Dehydration grade 3
Grade 2 toxicity
Renal grade 2
Anaemia grade 2
Constipation grade 2
Action dose reduction to Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2

Cycle 2 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity
Nil
Grade 2 toxicity
Dehydration grade 2
Diarrhoea grade 2
Alopecia grade 2
Action continue same dose

Cycle 3 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity
Nil
Grade 2 toxicity
Aneamia grade 2
Alopecia grade 2
Action continue same dose

Cycle 4 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 2 toxicity
Alopecia grade 2
Action continue same dose

Cycle 5 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity
Nil
Grade 2 toxicity
Alopecia grade 2
Action Dose reduction Taxotere 48mg/m2, Cisplatin 48mg/m2, 5FU 480mg/m2

Cycle 6
Grade 2 toxicity

Nausea	grade 3
Diarrhoea	grade 2
Alopecia	grade 2

COMPLETED TREATMENT

OVERALL RESPONSE	**PARTIAL RESPONSE**
TIME TO PROGESSION from last day of treatment	**6 weeks**
Overall Survival from last day of treatment	**20 weeks**

Patient 4 = TIN 4
Cycle 1 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity

Nausea	grade 3
Vomiting	grade 3
Diarrhoea	grade 3
Fatigue	grade 3 (in bed 2 weeks)
Anaemia	grade 3
mucositis	grade 3
Infection	**grade 4**
neutropenia	**grade 4**
dehydration	**grade 4**

Grade 2 toxicity

Alopecia	grade 2
Thrombocytopenia	grade 2
Action	Withdrawn from study

WITHDRAWN AFTER 1 CYCLE

OVERALL RESPONSE	**N/A**
TIME TO PROGESSION	**N/A**
Overall Survival	**11/09/09 to 4/06/10 = 29 weeks**

Patient 5= TIN 5
Cycle 5 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity

Fatigue	grade 3 (in bed 2 weeks)
Infection	**grade 4**
neutropenia	**grade 4**
dehydration	**grade 4**

Grade 2 toxicity

Alopecia	grade 2
Nausea	grade 2

Action Withdrawn from study

WITHDRAWN AFTER 1 CYCLE

OVERALL RESPONSE	**N/A**
TIME TO PROGESSION	**N/A**
Overall Survival	**24/09/09 to 10/01/10 = 15 weeks**

Patient 6=TIN 6
Cycle 1 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity

dehydration	grade 3

Grade 2 toxicity
Mucositis grade 2
pericarditis grade 2
Action continue same dose

Cycle 2 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity
nil
Grade 2 toxicity
alopecia grade 2
Action continue same dose

Cycle 3 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity
nil
Grade 2 toxicity
alopecia grade 2
Action continue same dose

Cycle 4 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity
nil
Grade 2 toxicity
alopecia grade 2
anaemia grade 2
Action continue same dose

Cycle 5 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 3 or 4 toxicity
Anaemia grade 3
Grade 2 toxicity
alopecia grade 2
mucositis grade 2
dehydration grade 2
Action continue same dose

Cycle 6 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2
Grade 2 toxicity
Alopecia grade 2
Action COMPLETED

COMPLETED TREATMENT
OVERALL RESPONSE **PARTIAL RESPONSE**
TIME TO PROGESSION from last day of treatment **9 weeks**
Overall Survival from last day of treatment **34weeks**

Patient 7= TIN 7
Cycle 1 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600/m2
Grade 3 or 4 toxicity
Mucositis grade 3
dehydration grade 3
Diarrhoea grade 3
renal dysfunction grade 3
hyperuracaemia grade 3(clinical gout)
Grade 2 toxicity
fatigue grade 2
Action dose reduction to Taxotere 48mg/m2, Cisplatin 48mg/m2, 5FU 480mg/m2

Cycle 2 Taxotere 48mg/m2, Cisplatin 48mg/m2, 5FU480/m2
Grade 3 or 4 toxicity
hyperuraeamia grade 3
Grade 2 toxicity
Mucositis grade 2
Vomiting grade 2
Diarrhoea grade 2
Action Taken off study as metastatic nodes in chest thought to be reactive as no change in size despite resolution in primary (now treated as neoadjuvant therapy prior to radical chemoradiotherapy

DMC review

The DMC met of the 13th January 2011. The Case report forms and Serious adverse event forms for each patient were reviewed. All trial radiology assessments were reviewed and clinical response and time to progression calculated (where relevant) for all patients. The committee determined that the study should close on the grounds of toxicity and futility.

Deaths, Serious Adverse Events, and Other Significant Adverse Events
Deaths

There were no deaths due to treatment. All patients had been withdrawn from the study due to cancer progression prior to death.

Serious Adverse events

There have been 9 SAE's in 7 patients while on study

5 directly related to the study medications in the opinion of the investigator
- 2 graded as life treating or severe
- 2 graded as moderate
- 1 graded as mild

3 probably related to study procedures
- 1 graded as life treating or severe
- 1 graded as moderate
- 1 graded as mild

1 related to the underlying illness
- 1 Graded as moderate

SAE's Directly related to Study medication

TIN 2

Diahorrea requiring admission following cycle 1 of (75mg/m2 Taxotere, 75mg/m2 Cisplatin, 750mg/m2 D1-4 5FU),
Graded as mild
Outcome – recovered without sequelae
Consequence - Dose reduction

TIN 2
Diahorroea dehydration neutropenia and sepsis following cycle 2 of TPF (60mg/m2 Taxotere, 60mg/m2 Cisplatin, 600mg/m2 D1-4 5FU), required admission
Graded as moderate
Outcome – recovered without sequelae
Consequence - Dose reduction (although in practice was withdrawn from study due to disease progression prior to cycle3)

TIN 3
Diahorroea, vomiting, dehydration following cycle 1 of TPF (75mg/m2 Taxotere, 75mg/m2 Cisplatin, 750mg/m2 D1-4 5FU), required admission for IV fluids
Graded as moderate
Outcome – recovered without sequelae
Consequence – Dose reduction

TIN 5
Diahorroea, vomiting, dehydration, neutropenia and sepsis following cycle 1 of TPF (60mg/m2 Taxotere, 60mg/m2 Cisplatin, 600mg/m2 D1-4 5FU), required admission medical HDU at RHH for ionotropic support.
Graded as life treating or severe
Outcome – recovered without sequelae
Consequence – Discontinues from study

TIN 7
Acute renal failure secondary to Diahorroea, vomiting, and dehydration cycle 1 of TPF (60mg/m2 Taxotere, 60mg/m2 Cisplatin, 600mg/m2 D1-4 5FU),
Graded as life treating or severe
Outcome – recovered without sequelae
Consequence – Dose reduction

SAE's Probabaley related to Study medication

TIN 4
LRTI, following cycle 1 of TPF (60mg/m2 Taxotere, 60mg/m2 Cisplatin, 600mg/m2 D1-4 5FU),
Graded as moderate
Outcome – recovered without sequelae
Consequence – given antibiotics

TIN 4
LRTI (readmitted day after discharge for previous SAE), sepsis, dehydration, hypoxia, following cycle 1 of TPF (60mg/m2 Taxotere, 60mg/m2 Cisplatin, 600mg/m2 D1-4 5FU),
Graded as life treating or severe
Outcome – recovered without sequelae
Consequence – Withdrawn from study

TIN 6
Chest pain – ? pericarditis on ECG, ? merely oesophagitis following cycle 1 of TPF (60mg/m2 Taxotere, 60mg/m2 Cisplatin, 600mg/m2 D1-4 5FU),
Graded as mild
Outcome – recovered without sequelae
Consequence – prescribed lanzoprazole

SAE's related to underlying disease

TIN 3
Developed symptoms of cord compression (not confirmed by MRI)

Graded as moderate
Outcome – recovered with sequelae
Consequence – Steroids, Analgesics

AE's

This was a pilot study to monitor toxicity and tolerability of cytotoxic chemotherapy. Toxicities were recorded at each clinic visit. All adverse events experienced were those as expected and are reported and listed in the results table
(See table of toxicities in results section).

Significant relation to demographic or other baseline features is not present.

Publications

A poster was presented at the 3rd Trends in Head and Neck Oncology Meeting. 3rd November 2011. Rome. (see appendix 5) Efforts will be made to publish the study results in a peer reviewed journal in 2012.
All participants in the study have since died so dissemination of results to participants in not possible .

Conclusions

The conclusion of this study is that the chemotherapy regime of Taxotere (Docetaxel) 60mg/m2 over 1 hr i.v. Day 1 plus Cisplatin i.v.60mg/m2 Day 1 over 2hrs plus 5FU 600 mg/m2 i.v. over 24hrs Day 1-4 on a 21 day cycle in adult patients with recurrent or metastatic carcinoma of the head and neck is considered to be too toxic for further study. Despite the use of prophylactic antibiotics Augmentin 625mg t.d.s. Days 7-16or Ciprofloxacin 500mg b.d. days 7-16 and G-CSF (Granocyte,Lenograstim) days 4-11.

Appendix 1

Taxotere in Palliative Therapy (TInPaT):

A Pilot Study of Taxotere (Docetaxel), Cisplatin and 5FU (TPF) in the Palliative Treatment of Squamous Cell Carcinoma of the Head and Neck.

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Taxotere in Palitative Therapy (TInPaT):

A pilot study of Taxotere (Docetaxel) Cisplatin and 5FU in the palliative treatment of squamous cell carcinoma of the head and neck.

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1. Background

1.1 Disease and Current Treatment

Head and neck cancer comprises approximately 3% of all cancer in the UK, with almost 5000 new cases annually[1]. Unlike many other tumour sites locoregional control almost equates with cure and for early disease control rates are high (80 - 90%). Unfortunately more than 70% of patients present with locoregionally advanced disease (stage III or IV) and despite aggressive local therapy with surgery, radiotherapy or both, many people develop recurrence. Before the advent of chemoradiotherapy and altered fractionation regimes, less than 30% of these patients remained disease free at 3 years [2]. Reported local control rates are now higher but the development of metastatic disease is a growing problem. The management of disseminated disease is often difficult, with few satisfactory treatments available. Traditionally squamous cell carcinoma of the head and neck has been thought of as resistant to chemotherapy, although a number of regimes have been used, with varying degrees of success. Methotrexate [3,6], bleomycin [4], FU [5] and cisplatin [7] have response rates of 10-25% as single agents in phase III clinical trials. Newer agents, such as the taxanes, have reported activity of 27-40% as a single agent in phase II studies but phase III trials are still required. Currently, despite the promise of newer agents, the "gold standard" treatment remains a combination of Cisplatin and 5FU, usually given as an infusion over 4 - 5 days. Although response rates of up to 75% have been reported for this combination given as first line therapy at presentation, only a 32% overall response is reported for recurrent head and neck cancer [5,6]. The benefits of chemotherapy remain modest and improvements in survival have not been clearly demonstrated in randomised trials. [7]

1.2 Rationale for the Addition of Taxotere (Docetaxel) to Cisplatin and 5FU for Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Cisplatin 100mg/m2 and 5FU 1000mg/m2 has been the gold standard regime for palliation of locally recurrent or metastatic squamous cell carcinoma of the head and neck for many years but there has been no documented survival benefit from this approach and treatment has been given purely for palliation of symptoms. The median survival following the development of recurrent or metastatic disease is approximately 6 months, with a 1 year survival of 20%. Taxotere (Docetaxel) has recently shown itself to be active in head and neck cancer and in neoadjuvant studies an overall survival benefit has been demonstrated. Addition of Taxotere (Docetaxel) to a combination of Cisplatin and 5FU as neoadjuvant therapy improved median survival from 14.5 months to 18.6 months in patients with unresectable squamous cell carcinoma of the head and neck treated by radical radiotherapy(excluding nasopharynx, nasal and paranasal cavities) . In this study the response rate for TPF was significantly greater than for cisplatin and 5FU alone, 67.9% vs 53.6% respectively (p=0.007)[8]. An improvement in response rate and overall median survival following the use of Taxanes in the recurrent or metastatic setting has also been suggested in a number of phase 2 studies[9,10,11]. In a small phase 2 study, Gedlicka et al demonstrated an overall response rate of 46.2% for the combination Cisplatin 75mg/m^2 and Taxotere (Docetaxel) 75mg/m^2 on day 1 of a 21 day cycle, in patients with recurrent or metastatic who had received primary treatment with chemoirradiation plus or minus surgery [9].

A Greek study indicated a 90% response rate of Taxotere (Docetaxel) , Cisplatin and 5FU when given as induction chemotherapy[13]. A further phase 2 study investigating the addition of paclitaxel to Cisplatin and 5 FU demonstrated an overall response rate of 58% in patients with recurrent or metastatic disease.[11] A study is required to investigate whether the addition of Taxotere (Docetaxel) to current treatments for locally recurrent metastatic carcinoma of the head and neck can be beneficial for patients in the metastatic setting in terms of overall survival and/or quality of life.

1.3 Rationale for performing the study

The lack of any chemotherapy with a proven record in prolonging life in advanced head and neck cancer makes it important to develop more effective drugs. In the EORTC neoadjuvant study in patients with inoperable squamous cell carcinoma of the head and neck the TPF regime was better tolerated that the cisplatin and 5FU (PF) arm, with 8.6% of patients experiencing a delay of more than 7 days in the chemotherapy schedule in the TPF arm versus 22.3% in the PF arm. Patients were also more likely to complete 4 cycles of TPF than 4 cycles of PF. While the incidence of neutropenia was higher in the TPF arm, with 75.3% developing grade 3 or 4 neutropenia compared to 50.8% in the PF arm, the incidence of infection in both arms was similar. Thrombocytopenia was more common with PF than TPF with 69% and 57% developing grade 3 or 4 thrombocytopenia respectively. Importantly the toxic death rate was lower in the TPF arm, 2.5% versus 5.5% in the PF arm. [8]. The lower toxicity profile of this combination and greater efficacy in the neoadjuvant situation raises the question whether this combination may be of benefit in the palliative setting.

A further phase 3 study, randomising 358 patients comparing TPF against Cisplatin and 5FU as neoadjuvant chemotherapy prior to radical surgery, investigated 4 cycles of Taxotere (Docetaxel) 75mg/m2 over 1 hr i.v. Day 1 plus Cisplatin i.v.75mg/m2 Day 1 over 4hrs and 5FU 750 mg/m2 i.v. over 24hrs Day 1-4, versus 4 cycles of Cisplatin 100mg/m2 on Day 1 plus 5FU 1000mg/m2 day 1-4 . This study indicated a statistically significant improvement in overall survival at a median follow up of 32 months (p=0.016).[9]

Before a phase 3 randomised study comparing TPF with the current gold standard can go ahead in the recurrent and metastatic setting, Taxotere (Docetaxel) , Cisplatin and 5FU needs to evaluated in a phase 2 study to establish the response rate and ensure its tolerability in this group of patients. Patients receiving chemotherapy for metastatic and recurrent disease tend to be of a lower performance status than those receiving radical therapy. In addition 45% of patients in the EORTC study had primary tumours of the oropharynx ; oropharyngeal primaries are known to be more chemosensitve and radiosensitive than primaries at other sites. In the metastatic setting oropharyngeal primaries may not represent such a high proportion of the study group.

This non commercial pilot study will investigate Taxotere (Docetaxel) 75mg/m2 over 1 hr i.v. Day 1 plus Cisplatin i.v.75mg/m2 Day 1 over 2hrs plus 5FU 750 mg/m2 i.v. over 24hrs Day 1-4. If this regime is found to be acceptable it will be trialed in a phase 3 study against standard Cisplatin and 5FU comparing quality of life and overall survival in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. This study is therefore a pilot study to assess tolerability of the study regime before embarking on a full phase 3 study.

The effect of the study regime on quality of life will be assessed using the EORTC QLQ 30 and H+N 35 questionnaires

2. Study Objectives

2.1 Primary Objectives

To determine the response rate (CR plus PR) and tolerability of Taxotere (Docetaxel) 75mg/m2 over 1 hr i.v. Day 1 plus Cisplatin i.v.75mg/m2 Day 1 over 2hrs plus 5FU 750 mg/m2 i.v. over 24hrs Day 1-4 (TPF) for the palliative treatment of squamous cell carcinoma of the head and neck.

2.2 Secondary Objectives

To assess the effect of TPF therapy on Quality of Life in this population

To assess the toxicity profile in this population.

To assess time to progression and survival status.

3.Duration of the Study

The required number of patients will be recruited to the study over a 12 month period

4. Selection Criteria

4.1 Total number of Patients

Initially 14 patients will be registered. The trial will then be suspended until data has been reviewed by an Independent Data Monitoring Committee (D.M.C.). If there is ≤1 response (PR or CR) then the study will stop. If are 2 or more toxic deaths attributable to chemotherapy amongst the initial 14 patients recruited to study, the study will close. If > 1 CR or PR is seen, then a further 11 patients will be recruited (Gehan stage 2 design). The Independent Data Monitoring Committee will confirm the response status of the first 14 patients entered in to the study and will give authorization for the trial to continue if the above criteria are met.
The D.M.C. will meet a minimum of 8 weeks after the 14th patient completing their treatment receives their final course of TPF.

4.2 Inclusion Criteria

Patients will be eligible for inclusion if the following criteria are met:

i) Aged over 18 and less than or equal to 70 at study entry

j) Histologically proven squamous carcinoma the head and neck, excluding carcinoma of the nasopharynx .

k) Patients must have disease that is considered unsuitable for radical treatment with either surgery or radiotherapy. Either or both forms of treatment may have been used previously in patients who have progressive disease but measurable disease recurrence must be present outside of a previously irradiated area if radiotherapy was completed within 6 months of randomisation.

l) Patients must be considered fit for chemotherapy.

m) ECOG performance status of 0,1 or 2.(appendix 4).

n) Able and willing to give written informed consent and to comply with the protocol for the duration of treatment and follow up.

o) Expected survival greater than 3 months from entry into study

p) Adequate renal function.

a. Calculated Cockroft/Gault GFR ≥ 60ml/min or
b. EDTA GFR ≥ 50ml/min

i) Measurable Disease. Defined as 1 measurable lesion where the longest diameter is ≥ 20mm on conventional CT or ≥ 10mm on spiral CT or MRI. or direct clinical measurement ≥ 10mm

4.3 Exclusion Criteria

i) Women who are lactating or pregnant.

j) Patients who have received previous chemotherapy for recurrent malignant disease or any cytotoxic chemotherapy within 6 months prior to study entry.

k) Patients who have received radiotherapy within 6 weeks or if they have ongoing acute radiotherapy toxicity.

l) A history of nervous or psychiatric disorder that would preclude informed consent or compliance with oral drug intake or treatment

m) A history of previous malignancy within the previous 5 years except successfully treated basal cell cancer of skin or carcinoma in situ of cervix.

n) Patients with the following laboratory values

1. Hb<10g/dl that cannot be corrected by blood transfusion.
2. Neutrophil count<1.5x 109/L
3. Platelets<100x109/L
4. Serum bilirubin >1.5xULN
5. ALT and/or AST>2.5xULN
6. Alkaline phosphatase>2.5xULN

o) Patients with uncontrolled infection.

p) Patients with a history of severe hypersensitivity reactions to Taxotere (Docetaxel) .

5. Assessment of Response and Toxicity

5.1 Assessments

Please see table in appendix 14.

Clinical assessment of the patient will be taken prior to each cycle, radiological assessments if required every 3 cycles. An assessment will be made 6 weeks following completion of therapy and every 6 weeks thereafter to 6 months. Then 3 monthly until tumour progression. The study will close 2 years after the last patient completes their treatment. There will be an analysis of data at one year after the last patient completes treatment or when all patients entered in to the study have progressive disease.

Staging will be based on clinical assessment and radiological investigations.

They will record prior to registration:

Medical history including medications
Full medical examination
Height, weight and BSA
FBC, Blood urea, creatinine and electrolytes, LFTs.
Creatinine Clearance (Cockroft and Gault Calculation)
Site and stage of disease
Dimensions of marker lesion - Assessment by CT or MRI (unless lesion palpable)

Patients will be assessed following each course of treatment as follows:

Clinical consultation.

Toxicities and adverse events will be recorded throughout treatment. Toxicities graded using NCIC Common Toxicity Criteria version 3.

FBC, Blood urea, creatinine and electrolytes, LFTs.

5.2 Primary and Secondary Outcome Measures

All patients who have at least two courses of TPF will be considered evaluable for efficacy analyses.

The primary outcome measure of the study is percentage response rate (CR and PR).

Secondary outcome measures median progression free survival, median overall survival, grade 3 and 4 toxicity rates (percentage) and changes in quality of life scores from baseline at 6 weeks following completion of chemotherapy.

5.3 Tumour Measurements

Tumours will be measured by the investigator in the most appropriate manner at baseline and at the end of course three and following cycle 6 . Reassessment of the tumour size will be performed using the same method used to establish baseline tumour measurements. Following completion of chemotherapy tumour measurements should be assessed clinically at each follow up visit. Radiological assessment should be performed as clinically indicated.

Lesions will be measured in millimetres.
A maximum of 5 target lesions per organ or a maximum of 10 lesions in total may be identified.

The sum of the longest diameter of all target lesions for all target lesions will be calculated at baseline and will be the reference when determining response. An estimate of overall objective and subjective response will be made and recorded each visit.

Measurable disease requires lesions with clearly defined margins and is **defined a minimum of one lesion where the longest diameter is ≥ 20mm on conventional CT or ≥ 10mm on spiral CT or MRI. or direct clinical measurement ≥ 10mm**

If an organ has too many measurable lesions to measure at each evaluation, five lesions will be selected for measurement at baseline.

5.4 Response Definitions

Complete Response (CR): Designation of CR requires all of the following. Complete disappearance of all target lesions. No new lesions appearing. Disappearance of all clinical signs and symptoms of cancer present at baseline.

Partial Response (PR): Designation of a PR requires all of the following. Greater than or equal to 30% decrease below baseline in the sum of the longest diameters of all target lesions (baseline as reference) . No new lesions or progression of disease occurring.

Stable/No Response (SD): Absence of any response or progression.

Progressive Disease (PD): A 20% or greater increase in the sum of the longest diameters of all target lesions over smallest sum observed as reference (over baseline if no decrease), OR reappearance of any lesion which had disappeared, OR appearance of any new lesion/site.

Time to response: Time from date of initial treatment until first objective documentation of response.

Duration of Response: Time from first objective documentation of response to first objective documentation of disease progression.

Time to Tumour Progression: Time from date of initial treatment to first objective documentation of progressive disease; follow-up will occur every six weeks until progression of the disease.

Treatment given after progression of disease shall be recorded.
In the event of the death, date of death and cause of death of the patient will also be recorded.

Best Evaluation Of Overall Response

Target Lesions	Non-Target lesions	New Lesions	Overall Response
CR	Complete resolution all lesions	nil	CR
CR	1 or more persisting lesions	nil	PR
PR	-	nil	PR
SD	-	nil	SD
PD	any	-	PD
any	New Lesions	-	PD
any	any	yes	PD

5.5 Quality of Life

The EORTC QLQ 30 and QLQ- H+N35 will be completed by the patient at study entry, at 6 weeks following completion of chemotherapy and every 3 months thereafter.
The patient may complete the QoL questionnaire at their hospital visit or they may take the questionnaire home and send it in to the hospital after completion. If the patient wishes to complete the questionnaire at the hospital visit a quiet private area should be provided to allow then to do so.

6. Study Design

6.1 Design

This is a Gehan design Phase II non randomised window study. The aim of the study is to establish response rates for TPF in the palliative treatment of head and neck cancer.

6.2 Randomisation

This is an open-label non-comparative study and therefore no randomisation procedure is involved.

6.3 Registration procedure and data monitoring

Up to 3 centres will be involved in the recruitment of patients. It is intended that suitable patients will be recruited as they present in order to recruit as rapidly as possible.

Patient recruitment will be controlled by the Sponsor who will co-ordinate patient registration. Each centre will be kept informed of the recruitment process.

All pre-treatment assessment must be completed before registration. Request for registration and confirmation of registration will be faxed.

7. Study medication

Day 1

Taxotere (Docetaxel) 75mg/m2 over 1 hr i.v.

N. Saline 1 lire over 2 hr

Manitol 20% 100mls over 15minutes

Cisplatin i.v.75mg/m2 Day 1 over 2hrs

N.Saline 1 litre over 2 hr plus Mg SO4 1g

plus

Day 2-5

5FU 750 mg/m2 i.v. over 24hrs (may be given as an outpatient via Hickman line and syringe driver)

Plus Augmentin 625mg t.d.s. Days 7-16or Ciprofloxacin 500mg b.d. days 7-16

Plus G-CSF (Granocyte,Lenograstim) days 4-11

Delivered on a 21 day cycle

Maximum of 6 cycles

Study drugs will be provided by respectable Pharmaceutical companies (Taxotere (Docetaxel) – Aventis and G-CSF - Chugi)Taxotere (Docetaxel) will be provided free of charge to participating centres upon registration through the Sponsor. 50% of G-CSF required will be provided directly from Churgi when the study chemotherapy prescription is received by the pharmacy department (oncology pharmacist to liase directly with Churgi area sales representative.

Supportive Medications

Antiemetics

A 5HT3 antagonist and dexamethasone combination should be given as the participating centres policy for highly emetogenic regimes.

A combination of Emend, 5HT3 antagonist and dexamethasone may also be used.

Dexamethasone

Dexamethasone 8mg twice a day for 3 days should be prescribed to commence 24 hours before delivery of Taxotere to prevent allergic reaction to Taxotere

8. Acute Toxicity

Toxicity will be assessed every twenty-one days during TPF therapy and at 6 weeks following completion of chemotherapy . Toxicity will be graded using NCIC Common Toxicity Criteria version 3.

9. Chemotherapy Dose Scheduling Modifications[18]

9.1) Treatment Modifications During Chemotherapy
Heamatological

For patients whose nadir of platelet count during the previous course of therapy is <25000 cells/mm^3, or in patients who experience febrile neutropenia the doses of cytotoxic drugs for the next cycle are to be reduced by 20% (80% of starting dose). If there is a further febrile neutropenic event or platelet nadir of <25000 cells/mm^3 in the following cycle of TPF the Taxotere should be discontinued.

9.2)Stomatitis and Diarrhoea

Cisplatin starting dose to be maintained.

Toxicity NCIC Grade*	During a course of Therapy	Dose adjustment-Taxotere (Docetaxel) and 5FU only for next cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance 2nd appearance 3rd appearance 4th appearance	Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue permanently	100% 80% 50%
Grade 3		
1st appearance 2nd appearance 3rd appearance	Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue permanently	80% 50%
Grade 4	Discontinue permanently	

9.3)Peripheral Neuropathy

Following development of a grade 3 or 4 peripheral neuropathy Cisplatin and Taxotere (Docetaxel) chemotherapy should be terminated and the patients withdrawn from the study.

9.4)Other

Toxicity NCIC Grade*	During a course of Therapy	Dose adjustment-all Drugs for next cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance 2nd appearance 3rd appearance 4th appearance	Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue permanently	100% 80% 50%
Grade 3		
1st appearance 2nd appearance 3rd appearance	Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue permanently	80% 50%
Grade 4	Discontinue permanently	

9.2 Adverse events

Expected adverse events that are **not** classed as serious **and** recorded and graded on the data collection forms as toxicity secondary to TPF i.e.

Nausea
Vomiting
Diarrhoea
Constipation
Mucositis
Anaemia
Neutropenia
Thrombocytopenia
Alopecia
Renal Dysfunction
Hepatic Dysfunction
Peripheral Neuropathy
Fatigue

do not need to be reported to the sponsor. All other adverse events must be reported to the sponsor by faxing the adverse event form to Dr Brammer on 01902 695624 .

10. Statistical Considerations and Analytical Plan

10.1 Sample Size.

Defined in section 6.1

This is a pilot study. The study is being ran prior to the development of a phase 3 study to ensure safety and tolerability. The response rates and toxicities will be expressed as a simple percentage only.

10.2 Analytical plan
All patients who start chemotherapy will be included in the final analysis. The following details will be summarised.

Patient demographics and tumour characteristics
Response rate
Details of the incidence of the toxicities.
Total number of cycles of TPF given
Number of TPF suspensions with reasons; duration of suspensions
Reasons for complete discontinuation of TPF
Details of the worst recorded grade of toxicities (including laboratory abnormalities) over the course of the study.
Changes in Quality of Life scores at 6 weeks after completion of chemotherapy from baseline and over the duration of the study.

The final results of the study will be submitted for publication in a peer reviewed journal and will be submitted for conference presentation.

11. Study Drugs
11.1 Taxotere (Docetaxel)
Route of Administration

Premedication
Premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting 1 day prior to Taxotere (Docetaxel) administration, unless contraindicated, can be used (see section 4.4).

Dosage adjustments during treatment:

General

Taxotere (Docetaxel) should be administered when the neutrophil count is ≥ 1,500 cells/mm^3. In patients who experienced either febrile neutropenia, neutrophil < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during Taxotere (Docetaxel) therapy, the dose of Taxotere (Docetaxel) should be reduced. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

In combination with cisplatin:

For patients who are dosed initially at Taxotere (Docetaxel) 75 mg/m^2 in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is <25000

cells/mm^3, or in patients who experience febrile neutropenia, or in patients with serious non-haematologic toxicities, the Taxotere (Docetaxel) dosage in subsequent cycles should be reduced to 60 mg/m^2. For cisplatin dosage adjustments, see manufacturer's summary of product characteristics

Patients who experience Grade 3 or 4 stomatitis should have their dose decreased as protocol dictates.

Special populations:

Patients with hepatic impairment: Based on pharmacokinetic data with Taxotere (Docetaxel) at 100 mg/m² as single agent, patients who have both elevations of transaminase (ALT and/or AST) greater than 1.5 times the upper limit of the normal range (ULN) and alkaline phosphatase greater than 2.5 times the ULN, the recommended dose of Taxotere (Docetaxel) is 75 mg/m^2 (see sections 4.4 and 5.2). For those patients with serum bilirubin >ULN and/or ALT and AST >3.5 times the ULN associated with alkaline phosphatase >6 times the ULN, no dose-reduction can be recommended and Taxotere (Docetaxel) should not be used unless strictly indicated. No data are available in patients with hepatic impairment treated by Taxotere (Docetaxel) in combination.

Elderly: Based on a population pharmacokinetic analysis, there are no special instructions for use in the elderly.

Contraindications

Hypersensitivity reactions to the active substance or to any of the excipients.
Taxotere (Docetaxel) should not be used in patients with baseline neutrophil count of <1,500 cells/mm^3.
Taxotere (Docetaxel) must not be used in pregnant or breast-feeding women.
Taxotere (Docetaxel) should not be used in patients with severe liver impairment since there is no data available (see sections 4.4 and 4.2).
Contraindications for other medicinal products also apply, when combined with Taxotere (Docetaxel) .

Special warnings and precautions for use

Premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g. 8 mg BID) for 3 days starting 1 day prior to Taxotere (Docetaxel) administration, unless contraindicated, can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Haematology

Neutropenia is the most frequent adverse reaction of Taxotere (Docetaxel) . Neutrophil nadirs occurred at a median of 7 days but this interval may be shorter in heavily pre-treated patients. Frequent monitoring of complete blood counts should be conducted on all patients receiving

Taxotere (Docetaxel) . Patients should be retreated with Taxotere (Docetaxel) when neutrophils recover to a level ≥1,500 cells/mm^3
In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of Taxotere (Docetaxel) therapy, a reduction in dose for subsequent courses of therapy or the use of appropriate symptomatic measures are recommended

Hypersensitivity reactions

Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of Taxotere (Docetaxel) , thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of Taxotere (Docetaxel) and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with Taxotere (Docetaxel) .

Cutaneous reactions

Localised skin erythema of the extremities (palms of the hands and soles of the feet) with oedema followed by desquamation has been observed. Severe symptoms such as eruptions followed by desquamation which lead to interruption or discontinuation of Taxotere (Docetaxel) treatment were reported (see section 4.2).

Fluid retention

Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascites should be monitored closely.

Patients with liver impairment

In patients treated with Taxotere (Docetaxel) at 100 mg/m^2 as single agent who have serum transaminase levels (ALT and/or AST) greater than 1.5 times the ULN concurrent with serum alkaline phosphatase levels greater than 2.5 times the ULN, there is a higher risk of developing severe adverse reactions such as toxic deaths including sepsis and gastrointestinal haemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. Therefore, the recommended dose of Taxotere (Docetaxel) in those patients with elevated liver function test (LFTs) is 75 mg/m^2 and LFTs should be measured at baseline and before each cycle (see section 4.2).
For patients with serum bilirubin levels >ULN and/or ALT and AST >3.5 times the ULN concurrent with serum alkaline phosphatase levels >6 times the ULN, no dose-reduction can be recommended and Taxotere (Docetaxel) should not be used unless strictly indicated.
No data are available in patients with hepatic impairment treated by Taxotere (Docetaxel) in combination.

Patients with renal impairment

There are no data available in patients with severely impaired renal function treated with Taxotere (Docetaxel) .

Nervous system

The development of severe peripheral neurotoxicity requires a reduction of dose (see section 9.3

Others

Contraceptive measures must be taken during and for at least three months after cessation of therapy.

Interactions

There have been no formal clinical studies to evaluate the drug interactions of Taxotere (Docetaxel) .
In vitro studies have shown that the metabolism of Taxotere (Docetaxel) may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as ciclosporine, terfenadine, ketoconazole, erythromycin and troleandomycin. As a result, caution should be exercised when treating patients with these drugs as concomitant therapy since there is a potential for a significant interaction.
Taxotere (Docetaxel) is highly protein bound (>95%). Although the possible *in vivo* interaction of Taxotere (Docetaxel) with concomitantly administered medication has not been investigated formally, *in vitro* interactions with tightly protein-bound drugs such as erythromycin, diphenhydramine, propranolol, propafenone, phenytoin, salicylate, sulfamethoxazole and sodium valproate did not affect protein binding of Taxotere (Docetaxel) . In addition, dexamethasone did not affect protein binding of Taxotere (Docetaxel) . Taxotere (Docetaxel) did not influence the binding of digoxin.
The pharmacokinetics of Taxotere (Docetaxel) , doxorubicin and cyclophosphamide were not influenced by their coadministration. Limited data from a single uncontrolled study were suggestive of an interaction between Taxotere (Docetaxel) and carboplatin. When combined to Taxotere (Docetaxel) , the clearance of carboplatin was about 50% higher than values previously reported for carboplatin monotherapy.
Taxotere (Docetaxel) pharmacokinetics in the presence of prednisone was studied in patients with metastatic prostate cancer. Taxotere (Docetaxel) is metabolised by CYP3A4 and prednisone is known to induce CYP3A4. No statistically significant effect of prednisone on the pharmacokinetics of Taxotere (Docetaxel) was observed.

Undesirable effects

The adverse reactions considered to be possibly or probably related to the administration of TAXOTERE (Docetaxel) have been obtained in:.
• 1312 and 121 patients who received 100 mg/m² and 75 mg/m² of TAXOTERE (Docetaxel) as a single agent respectively
• 258 patients who received TAXOTERE (Docetaxel) in combination with doxorubicin
• 406 patients who received TAXOTERE (Docetaxel) in combination with cisplatin

• 92 patients treated with TAXOTERE (Docetaxel) in combination with trastuzumab,
• 255 patients who received TAXOTERE (Docetaxel) in combination with capecitabine,
• 332 patients who received TAXOTERE (Docetaxel) in combination with prednisone or prednisolone (clinically important treatment related adverse events are presented).
• 744 patients who received TAXOTERE (Docetaxel) in combination with doxorubicin and cyclophosphamide (clinically important treatment related adverse events are presented).
These reactions were described using the NCI Common Toxicity Criteria (grade 3 = G3; grade 3-4 = G3/4; grade 4 = G4) and the COSTART terms. Frequencies are defined as: very common (>1/10), common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000).
The most commonly reported adverse reaction was neutropenia, which was reversible and not cumulative (see sections 4.2 and 4.4). The median day to nadir was 7 days and the median duration of severe neutropenia (<500 cells/mm^3) was 7 days."

Neoplasms benign and malignant (including cysts and polyps)

Two patients were diagnosed with leukaemia at a median follow-up time of 55 months and one case of leukaemia was reported after the follow-up period. No cases of myelodysplastic syndrome occurred.

Blood and the lymphatic system disorders

Bone marrow suppression and other hematologic adverse reactions have been reported.

TAXOTERE (Docetaxel) 100mg/m² single agent:

Very common: Neutropenia (96.6%; G4: 76.4%); Anaemia (90.4%; G3/4: 8.9%); Infections (20%; G3/4: 5.7%, including sepsis and pneumonia, fatal in 1.7%); Febrile neutropenia (11.8%).
Common: Thrombocytopenia (7.8%; G4: 0.2%); G3/4 infection associated with neutrophil count <500 cells/mm^3 (4.6%); Bleeding episodes (2.4%).
Rare: Bleeding episodes associated with G3/4 thrombocytopenia.

TAXOTERE (Docetaxel) 75mg/m² single agent:

Very common: Neutropenia (89.8%; G4: 54.2%); Anaemia (93.3%; G3/4: 10.8%); Infections (10.7%; G3/4: 5%); Thrombocytopenia (10%; G4: 1.7%).
Common: Febrile neutropenia (8.3%).

TAXOTERE (Docetaxel) 75mg/m² in combination with cisplatin:

Very common: Neutropenia (91.1%; G4: 51.5%); Anaemia (88.6%; G3/4: 6.9%); Fever in absence of infection (17.2%; G3/4:1.2%); Thrombocytopenia (14.9%; G4: 0.5%); Infections (14.3%; G3/4: 5.7%).
Common: Febrile neutropenia (4.9%).

Immune system disorders

Hypersensitivity reactions have generally occurred within a few minutes following the start of the infusion of Taxotere (Docetaxel) and were usually mild to moderate. The most frequently reported symptoms were flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and drug fever or chills. Severe reactions, characterised by hypotension and/or bronchospasm or generalized rash/erythema, resolved after discontinuing the infusion and appropriate therapy (see section 4.4).

TAXOTERE (Docetaxel) 75mg/m² single agent: common (2.5%, no severe)
TAXOTERE (Docetaxel) 75mg/m² in combination with cisplatin: very common (10.6%; G3/4: 2.5%)

Skin and subcutaneous tissue disorders

Reversible cutaneous reactions have been observed and were generally considered as mild to moderate. Reactions were characterised by a rash including localised eruptions mainly on the feet and hands (including severe hand and foot syndrome), but also on the arms, face or thorax, and frequently associated with pruritus. Eruptions generally occurred within one week after the Taxotere (Docetaxel) infusion. Less frequently, severe symptoms such as eruptions followed by desquamation which rarely lead to interruption or discontinuation of Taxotere (Docetaxel) treatment were reported (see sections 4.2 and 4.4). Severe nail disorders are characterised by hypo- or hyperpigmentation and sometimes pain and onycholysis. Very rare cases of bullous eruption such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, have been reported with Taxotere (Docetaxel) and other concomitant factors may have contributed to the development of these effects.

TAXOTERE (Docetaxel) 75mg/m² single agent:

Very common: Alopecia (38%); Cutaneous reactions (15.7%; G3/4: 0.8%).
Common: Nail changes (9.9%; severe 0.8%).

TAXOTERE (Docetaxel) 75mg/m² in combination with cisplatin:

Very common: Alopecia (73.6%); Nail changes (13.3%; severe 0.7%); Cutaneous reactions (11.1%; G3/4: 0.2%)
Alopecia was observed to be ongoing at the median follow-up time of 55 months in 22 patients out of the 687 patients with alopecia at the end of the chemotherapy.

Fluid retention

Events such as peripheral oedema and less frequently pleural effusion, pericardial effusion, ascites and weight gain have been reported. The peripheral oedema usually starts at the lower extremities and may become generalised with a weight gain of 3 kg or more. Fluid retention is cumulative in incidence and severity (see section 4.4).
TAXOTERE (Docetaxel) 75mg/m² single agent: very common (24.8%; severe 0.8%)

TAXOTERE (Docetaxel) 75mg/m² in combination with doxorubicin: very common (35.7%; severe 1.2%)
TAXOTERE (Docetaxel) 75mg/m² in combination with cisplatin: very common (25.9%; severe 0.7%)

Gastrointestinal disorders

TAXOTERE (Docetaxel) 75mg/m² single agent:

Very common: Nausea (28.9%; G3/4: 3.3%); Stomatitis (24.8%; G3/4: 1.7%); Vomiting (16.5%; G3/4: 0.8%); Diarrhoea (11.6%; G3/4: 1.7%).
Common: Constipation (6.6%).

TAXOTERE (Docetaxel) 75mg/m² in combination with cisplatin:

Very common: Nausea (69%; G3/4:9.6%); Vomiting (53.4%; G3/4: 7.6%); Diarrhoea (41.1%; G3/4: 6.4%); Stomatitis (23.4%; G3/4: 2%);.
Common: Constipation (9.4%).
.

Nervous system disorders

The development of severe peripheral neurotoxicity requires a reduction of dose Mild to moderate neuro-sensory signs are characterised by paresthesia, dysesthesia or pain including burning. Neuro-motor events are mainly characterised by weakness.

TAXOTERE (Docetaxel) 75mg/m² single agent:

Very common: Neurosensory (24%; G3: 0.8%).
Common: Neuromotor (9.9%; G3/4: 2.5%).

TAXOTERE (Docetaxel) 75mg/m² in combination with cisplatin:

Very common: Neurosensory (40.4%; G3:3.7%), Neuromotor (12.8%; G3/4: 2%)
.
Rare cases of convulsion or transient loss of consciousness have been observed with Taxotere (Docetaxel) administration. These reactions sometimes appear during the infusion of the drug.

Cardiac disorders

TAXOTERE (Docetaxel) 75mg/m² single agent:

Common: Cardiac dysrhythmia (2.5%, no severe); Hypotension (1.7%).

TAXOTERE (Docetaxel) 75mg/m² in combination with cisplatin:

Common: Hypotension (3.7%; G3/4: 0.7%); Cardiac dysrhythmia (2.5%; G3/4: 0.7%).
Uncommon: Heart failure (0.5%)
%).

Vascular disorders

Venous thromboembolic events have rarely been reported.

Hepato-biliary disorders

TAXOTERE (Docetaxel) 75mg/m² single agent:

Common: G3/4 bilirubin increase (<2%).

TAXOTERE (Docetaxel) 75mg/m² in combination with cisplatin:

Common: G3/4 bilirubin increase (2.1%); G3/4 ALT increase (1.3%).
Uncommon: G3/4 AST increase (0.5%); G3/4 alkaline phosphatase increase (0.3%).

Metabolism and nutrition disorders

TAXOTERE (Docetaxel) 75mg/m² single agent: Very common: Anorexia (19%).

TAXOTERE (Docetaxel) 75mg/m² in combination with cisplatin: Very common: Anorexia (28.8%).

Eye Disorders

Very rare cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during drug infusion and in association with hypersensitivity reactions have been reported. These were reversible upon discontinuation of the infusion.
Cases of lacrimation with or without conjunctivitis, as cases of lacrimal duct obstruction resulting in excessive tearing have been rarely reported.

Musculoskeletal, connective tissue and bone disorders

TAXOTERE (Docetaxel) 75mg/m² single agent:

Common: Myalgia (5.8%).

TAXOTERE (Docetaxel) 75mg/m² in combination with cisplatin:

Very common: Myalgia (13.8%; severe 0.5%).

General disorders and administration site conditions

Infusion site reactions were generally mild and consisted of hyper pigmentation, inflammation, redness or dryness of the skin, phlebitis or extravasation and swelling of the vein.

TAXOTERE (Docetaxel) 75mg/m² single agent:

Very common: Asthenia (48.8%; severe 12.4%); Pain (10.7%).

TAXOTERE (Docetaxel) 75mg/m² in combination with doxorubicin:

Very common: Asthenia (54.7%; severe 8.1%); Pain (17.1%).
Common: Infusion site reaction (3.1%).

TAXOTERE (Docetaxel) 75mg/m² in combination with cisplatin:

Very common: Asthenia (51.5%; severe 9.9%).
Common: Infusion site reaction (6.2%); Pain (5.4%).

Radiation recall phenomena have rarely been reported.

Pharmacological properties

Preclinical data

Taxotere (Docetaxel) is an antineoplastic agent which 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 Taxotere (Docetaxel) to microtubules does not alter the number of protofilaments.
Taxotere (Docetaxel) has been shown *in vitro* to disrupt the microtubular network in cells which is
essential for vital mitotic and interphase cellular functions.
Taxotere (Docetaxel) was found to be cytotoxic *in vitro* against various murine and human tumour cell lines and against freshly excised human tumour cells in clonogenic assays. Taxotere (Docetaxel) achieves high intracellular concentrations with a long cell residence time. In addition, Taxotere (Docetaxel) was found to be active on some but not all cell lines over expressing the p-glycoprotein which is encoded by the multidrug resistance gene. *In vivo*, Taxotere (Docetaxel) is schedule independent and has a broad spectrum of experimental antitumour activity against advanced murine and human grafted tumours.

Pharmacokinetics
The pharmacokinetics of Taxotere (Docetaxel) have been evaluated in cancer patients after administration of 20-115 mg/m^2 in Phase I studies. The kinetic profile of Taxotere (Docetaxel) is dose independent and consistent with a three-compartment pharmacokinetic model with half lives for the a, b and g phases of 4 min, 36 min and 11.1 h, respectively. The late phase is due, in

part, to a relatively slow efflux of Taxotere (Docetaxel) from the peripheral compartment. Following the administration of a 100 mg/m^2 dose given as a one-hour infusion a mean peak plasma level of 3.7 µg/ml was obtained with a corresponding AUC of 4.6 h.µg/ml. Mean values for total body clearance and steady-state volume of distribution were 21 l/h/m^2 and 113 l, respectively. Inter individual variation in total body clearance was approximately 50%. Taxotere (Docetaxel) is more than 95% bound to plasma proteins.
A study of ^{14}C-Taxotere (Docetaxel) has been conducted in three cancer patients. Taxotere (Docetaxel) was eliminated in both the urine and faeces following cytochrome P450-mediated oxidative metabolism of the tert-butyl ester group, within seven days, the urinary and faecal excretion accounted for about 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in faeces is excreted during the first 48 hours as one major inactive metabolite and 3 minor inactive metabolites and very low amounts of unchanged drug.
A population pharmacokinetic analysis has been performed with Taxotere (Docetaxel) in 577 patients. Pharmacokinetic parameters estimated by the model were very close to those estimated from Phase I studies. The pharmacokinetics of Taxotere (Docetaxel) were not altered by the age or sex of the patient. In a small number of patients (n=23) with clinical chemistry data suggestive of mild to moderate liver function impairment (ALT, AST ≥1.5 times the ULN associated with alkaline phosphatase ≥2.5 times the ULN), total clearance was lowered by 27% on average (see section 4.2). Taxotere (Docetaxel) clearance was not modified in patients with mild to moderate fluid retention and there are no data available in patients with severe fluid retention.
When used in combination, Taxotere (Docetaxel) does not influence the clearance of doxorubicin and the plasma levels of doxorubicinol (a doxorubicin metabolite). The pharmacokinetics of Taxotere (Docetaxel) , doxorubicin and cyclophosphamide were not influenced by their coadministration.
Phase I study evaluating the effect of capecitabine on the pharmacokinetics of Taxotere (Docetaxel) and vice versa showed no effect by capecitabine on the pharmacokinetics of Taxotere (Docetaxel) (Cmax and AUC) and no effect by Taxotere (Docetaxel) on the pharmacokinetics of a relevant capecitabine metabolite 5'-DFUR.
Clearance of Taxotere (Docetaxel) in combination therapy with cisplatin was similar to that observed following monotherapy. The pharmacokinetic profile of cisplatin administered shortly after TAXOTERE (Docetaxel) infusion is similar to that observed with cisplatin alone

The effect of prednisone on the pharmacokinetics of Taxotere (Docetaxel) administered with standard dexamethasone premedication has been studied in 42 patients. No effect of prednisone on the pharmacokinetics of Taxotere (Docetaxel) was observed.

Pharmaceutical paticulars
List of excipients
TAXOTERE (Docetaxel) vial: polysorbate 80.
Solvent vial: ethanol in water for injections
Incompatibilities
non known
Shelf life

TAXOTERE (Docetaxel) 20mg vials: 2 years
TAXOTERE (Docetaxel) 80mg vials: 36 months

Premix solution: The premix solution contains 10 mg/ml Taxotere (Docetaxel) and should be used immediately after preparation. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between 2°C and 8°C or at room temperature.
Infusion solution: the infusion solution should be used within 4 hours at room temperature

Special precautions for storage
Vials should be stored between 2°C and 25°C and protected from bright light.
Nature and contents of container
Each blister carton of TAXOTERE (Docetaxel) 20 mg or 80 mg concentrate and solvent for solution for infusion contains:
• one single-dose TAXOTERE (Docetaxel) vial and,
• one single-dose solvent for TAXOTERE (Docetaxel) vial

TAXOTERE (Docetaxel) 20 mg concentrate for solution for infusion vial:

The TAXOTERE (Docetaxel) 20 mg concentrate for solution for infusion vial is a 7 ml clear glass vial with a green flip-off cap.
This vial contains 0.5 ml of a 40 mg/ml solution of Taxotere (Docetaxel) in polysorbate 80 (fill volume: 24.4mg/0.61 ml). This fill volume has been established during the development of TAXOTERE (Docetaxel) to compensate for liquid loss during preparation of the premix due to foaming,
adhesion to the walls of the vial and "dead-volume". This overfill ensures that after dilution with the entire contents of the accompanying solvent for TAXOTERE (Docetaxel) vial, there is a minimal extractable premix volume of 2 ml containing 10 mg/ml Taxotere (Docetaxel) which corresponds to the labelled amount of 20 mg per vial.

Solvent vial:

The solvent vial is a 7 ml clear glass vial with a transparent colourless flip-off cap.
Solvent vial contains 1.5 ml of a 13% w/w solution of ethanol in water for injections (fill volume: 1.98 ml). The addition of the entire contents of the solvent vial to the contents of the TAXOTERE (Docetaxel) 20 mg concentrate for solution for infusion vial ensures a premix concentration of 10 mg/ml Taxotere (Docetaxel) .

TAXOTERE (Docetaxel) 80 mg concentrate for solution for infusion vial:

The TAXOTERE (Docetaxel) 80 mg concentrate for solution for infusion vial is a 15 ml clear glass vial with a red flip-off cap.
This vial contains 2 ml of a 40 mg/ml solution of Taxotere (Docetaxel) in polysorbate 80 (fill volume: 94.4 mg/2.36 ml). This fill volume has been established during the development of TAXOTERE (Docetaxel) to compensate for liquid loss during preparation of the premix due to foaming, adhesion to the walls of the vial and "dead-volume". This overfill ensures that after dilution with the entire contents of the accompanying solvent for TAXOTERE (Docetaxel) vial, there is a minimal extractable premix volume of 8 ml containing 10 mg/ml Taxotere (Docetaxel) which corresponds to the labelled amount of 80 mg per vial.

Solvent vial:

The solvent vial is a 15 ml clear glass vial with a transparent colourless flip-off cap.
Solvent vial contains 6 ml of a 13% w/w solution of ethanol in water for injections (fill volume: 7.33 ml). The addition of the entire contents of the solvent vial to the contents of the TAXOTERE (Docetaxel) 80 mg concentrate for solution for infusion vial ensures a premix concentration of 10 mg/ml Taxotere (Docetaxel) .

Instructions for use, handling and disposal

Recommendations for safe handling

TAXOTERE (Docetaxel) is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing TAXOTERE (Docetaxel) solutions. The use of gloves is recommended.
If TAXOTERE (Docetaxel) concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If TAXOTERE (Docetaxel) concentrate, premix solution or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Preparation for the intravenous administration

a) Preparation of the TAXOTERE (Docetaxel) premix solution (10 mg Taxotere (Docetaxel) /ml)

If the vials are stored under refrigeration, allow the required number of TAXOTERE (Docetaxel) boxes to stand at room temperature for 5 minutes.
Using a syringe fitted with a needle, aseptically withdraw the entire contents of the solvent for TAXOTERE (Docetaxel) vial by partially inverting the vial.
Inject the entire contents of the syringe into the corresponding TAXOTERE (Docetaxel) vial.
Remove the syringe and needle and mix manually by repeated inversions for at least 45 seconds. Do not shake.
Allow the premix vial to stand for 5 minutes at room temperature and then check that the solution is homogenous and clear (foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation).
The premix solution contains 10 mg/ml Taxotere (Docetaxel) and should be used immediately after preparation. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between 2°C and 8°C or at room temperature.

b) Preparation of the infusion solution

More than one premix vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, aseptically withdraw the corresponding premix volume containing 10 mg/ml Taxotere (Docetaxel) from the appropriate number of premix vials using graduated syringes fitted with a needle. For example, a dose of 140 mg Taxotere (Docetaxel) would require 14 ml Taxotere (Docetaxel) premix solution.
Inject the required premix volume into a 250 ml infusion bag or bottle containing either 5% glucose solution or 0.9% sodium chloride solution.
If a dose greater than 200 mg of Taxotere (Docetaxel) is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml Taxotere (Docetaxel) is not exceeded.

Mix the infusion bag or bottle manually using a rocking motion.
The TAXOTERE (Docetaxel) infusion solution should be used within 4 hours and should be aseptically administered as a 1-hour infusion under room temperature and normal lighting conditions.
As with all parenteral products, TAXOTERE (Docetaxel) premix solution and infusion solution should be visually inspected prior to use, solutions containing a precipitate should be discarded.

Disposal

All materials that have been utilised for dilution and administration should be disposed of according to standard procedures.

11.2 Cisplatin

method of administration
Route of administration: Intravenous infusion.

Special warnings and precautions for use
Cisplatin is contra-indicated in patients who have previous allergic reactions to Cisplatin or other platinum compounds as anaphylactic-like reactions have been reported. Relative contra-indications are pre-existing renal impairment, hearing disorders and depressed bone marrow function which may increase toxicity.

This agent should only be administered under the direction of physicians experienced in cancer chemotherapy.
Renal function: Cisplatin produces cumulative nephrotoxicity. Renal function and serum electrolyte (magnesium, sodium, potassium and calcium) should be evaluated prior to initiating cisplatin treatment and prior to each subsequent course of therapy.

Repeat courses of Cisplatin should not be given unless renal function has been assessed. For this study Cockcroft Gault calculated GFR should be ≥60ml/min or EDTA GFR ≥ 50ml/min
Special care has to be taken when cisplatin-treated patients are given concomitant therapies with other potentially nephrotoxic drugs (See also section 4.5 'Interaction with other medicinal products and other forms of Interaction').
In addition, adequate post-treatment hydration and urinary output should be monitored. Concomitant use of nephrotoxic drugs may seriously impair kidney function.
Bone marrow function: Peripheral blood counts should be monitored frequently in patients receiving Cisplatin. Although the haematologic toxicity is usually moderate and reversible, severe thrombocytopenia and leucopenia may occur. In patients who develop thrombocytopenia special precautions are recommended: care in performing invasive procedures; search for signs of bleeding or bruising; test of urine, stools and emesis for occult blood, avoiding aspirin and other NSAIDs. Patients who develop leucopenia should be observed carefully for signs of infection and might require antibiotic support and blood product transfusions.
Hearing function: Cisplatin may produce cumulative ototoxicity, which is more likely to occur with high-dose regimens. Audiometry should be performed prior to initiating therapy, and repeated audiograms should be performed when auditory symptoms occur or clinical hearing changes become apparent. Clinically important deterioration of auditive function may require dosage modifications or discontinuation of therapy.

*CNS functions:*Cisplatin is known to induce neurotoxicity; therefore, neurologic examination is warranted in patients receiving a cisplatin-containing treatment. Since neurotoxicity may result in irreversible damage, it is recommended to discontinue therapy with Cisplatin when neurologic toxic signs or symptoms become apparent.
Anaphylactic-like reactions to Cisplatin have been observed. These reactions can be controlled by administration of antihistamines, adrenaline and/or glucocorticoids.
Neurotoxicity secondary to Cisplatin administration has been reported and therefore neurological examinations are recommended. Cisplatin has been shown to be mutagenic. It may also have an anti-fertility effect. Other anti-neoplastic substances have been shown to be carcinogenic and this possibility should be borne in mind in long term use of Cisplatin.
Liver function should also be monitored periodically.

Interaction with other medicinal products and other forms of interaction
Cisplatin is mostly used in combination with antineoplastic drugs having similar cytotoxic effects. In these circumstances additive toxicity is likely to occur.
Nephrotoxic drugs: Aminoglycoside antibiotics, when given concurrently or within 1-2 weeks after cisplatin administration, may potentiate its nephrotoxic effects. Concomitant use of other potentially nephrotoxic drugs (e.g. amphotericin B) is not recommended during Cisplatin therapy.
Ototoxic drugs: Concurrent and/or sequential administration of ototoxic drugs such as aminoglycoside antibiotics or loop diuretics may increase the potential of Cisplatin to cause ototoxicity, especially in the presence of renal impairment.
Renally excreted drugs: Literature data suggest that Cisplatin may alter the renal elimination of bleomycin and methotrexate (possibly as a result of cisplatin-induced nephrotoxicity) and enhance their toxicity.
Anticonvulsant agents: In patients receiving Cisplatin and phenytoin, serum concentrations of the latter may be decreased, possibly as a result of decreased absorption and/or increased metabolism. In these patients, serum levels of phenytoin should be monitored and dosage adjustments made as necessary.
Antigout agents: Cisplatin may raise the concentration of blood uric acid. Thus, in patients concurrently receiving antigout agents such as allopurinol, colchicine, probenecid or sulfinpyrazone, dosage adjustment of these drugs may be necessary to control hyperuricemia and gout.

Undesirable effects
Nephrotoxicity: Acute renal toxicity, which was highly frequent in the past and represented the major dose-limiting toxicity of Cisplatin, has been greatly reduced by the use of 6 to 8-hour infusions as well as by concomitant intravenous hydration and forced diuresis. Cumulative toxicity, however, remains a problem and may be severe. Renal impairment, which is associated with tubular damage, may be first noted during the second week after a dose and is manifested by an increase in serum creatinine, blood urea nitrogen, serum uric acid and/or a decrease in creatinine clearance. Renal insufficiency is generally mild to moderate and reversible at the usual doses of the drug (recovery occurring as a rule within 2-4 weeks); however, high or repeated Cisplatin doses can increase the severity and duration of renal impairment and may produce irreversible renal insufficiency (sometimes fatal). Renal failure has been reported also following intraperitoneal instillation of the drug.
Cisplatin may also cause serious electrolyte disturbances, mainly represented by hypomagnesemia, hypocalcemia, and hypokalemia, and associated with renal tubular

dysfunction. Hypomagnesemia and/or hypocalcemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpopedal spasm, and/or tetany. *Gastrointestinal toxicity:* Nausea and vomiting occur in the majority of Cisplatin-treated patients, usually starting within 1 hour of treatment and lasting up to 24 hours or longer.. These side effects are only partially relieved by standard antiemetics. The severity of these systems may be reduced by dividing the total dose per cycle into smaller doses given once daily for five days.
Haematologic toxicity: Myelosuppression often occurs during Cisplatin therapy, but is mostly mild to moderate and reversible at the usual doses. Leucopenia is dose-related, possibly cumulative, and usually reversible. The onset of leucopenia occurs usually between days 6 and 26 and the time of recovery ranges from 21 to 45 days. Thrombocytopenia is also a dose-limiting effect of Cisplatin but is usually reversible. The onset of thrombocytopenia is usually from days 10 to 26 and the time of recovery ranges from about 28 to 45 days.
The incidence of Cisplatin-induced anaemia (haemoglobin drop of 2 g/100 ml) ranges from 9% to 40%, although this is a difficult toxic effect to assess because it may have a complex aetiology in cancer patients.
There have been rare reports of acute myelogenous leukemias and myelodysplastic syndromes arising in patients who have been treated with Cisplatin, mostly when given in combination with other potentially leukomogenic agents.
Ototoxicity: Unilateral or bilateral tinnitus, with or without hearing loss, occurs in about 10% of Cisplatin-treated patients and is usually reversible. The damage to the hearing system appears to be dose-related and cumulative, and it is reported more frequently in very young and very old patients.
The overall incidence of audiogram abnormalities is 24%, but large variations exist. These abnormalities usually appear within 4 days after drug administration and consist of at least a 15 decibel loss in pure tone threshold. . The audiogram abnormalities are most common in the 4000-8000 Hz frequencies.
Neurotoxicity: Peripheral neuropathies occur infrequently with usual doses of the drug. These are generally sensory in nature (e.g. paresthesia of the upper and lower extremities) but can also include motor difficulties, reduced reflexes and leg weakness. Autonomic neuropathy, seizures, slurred speech, loss of taste and memory loss have also been reported. These neuropathies usually appear after prolonged therapy, but have also developed after a single drug dose. Peripheral neuropathy may be irreversible in some patients; however, it has been partially or completely reversible in others following discontinuance of Cisplatin therapy.
Hypersensitivity: Anaphylactic and anaphylactic-like reactions, such as flushing, facial oedema, wheezing, tachycardia and hypotension, have been occasionally reported. These reactions may occur within a few minutes after intravenous administration. Antihistamine, adrenaline and/or glucocorticoids control all these reactions. Rarely, urticarial or maculopapular skin rashes have also been observed.
Ocular toxicity: Optic neuritis, papilloedema, and cortical blindness have been reported rarely in patients receiving Cisplatin. These events are usually reversible after drug withdrawal.
Hepatotoxicity: Mild and transient elevations of serum AST and ALT levels may occur infrequently.
Other toxicities: Other reported toxicities are:
cardiovascular abnormalities (coronary artery disease, congestive heart failure, arrhythmias, postural hypotension, thrombotic microangiopathy, etc), hyponatremia / syndrome of inappropriate antidiuretic hormone (SIADH)), mild alopecia, myalgia, pyrexia and gingival platinum line. Pulmonary toxicity has been reported in patients treated with Cisplatin in combination with bleomycin or 5-fluorouracil.

Hyperuricaemia: Hyperuricaemia occurring with Cisplatin is more pronounced with doses greater than 50 mg/m^2. Allopurinol effectively reduces uric acid levels.
Hypomagnesemia: Asymptomatic hypomagnesemia has been documented in a certain number of patients treated with Cisplatin, symptomatic hypomagnesemia has been observed in a limited number of cases.
Thromboembolism: Cancer patients are generally at an increased risk for thromboembolic events. Cerebrovascular accidents (e.g. haemorrhagic and ischaemic stroke, amaurosis fugax, sagittal sinus thrombosis) have been observed in patients receiving Cisplatin therapy.
Local effects such as phlebitis, cellulitis and skin necrosis (following extravasation of the drug) may also occur.
Cisplatin can affect male fertility. Impairment of spermatogenesis and azoospermia have been reported. Although the impairment of spermatogenesis can be reversible, males undergoing Cisplatin treatment should be warned about the possible adverse effects on male fertility.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
In vitro studies indicate that DNA is the principal target molecule of cis-platinum.
The basis for the selectivity of the cis-isomer may reside in its ability to react in a specifically defined configuration with DNA.

11.3 5 – Fluorouracil

method of administration
Route of administration: Intravenous infusion.

Special warnings and precautions for use
It is recommended that Fluorouracil be given only by, or under the strict supervision of, a qualified physician who is conversant with the use of potent antimetabolites.
All patients should be admitted to hospital for initial treatment.
Adequate treatment with Fluorouracil is usually followed by leucopenia, the lowest white blood cell (W.B.C) count commonly being observed between the 7th and 14th day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the 30th day. The ratio between effective and toxic dose is small and therapeutic response is unlikely without some degree of toxicity. Care must be taken therefore, in the selection of patients and adjustment of dosage.
Flourouracil should be used with caution in patients with reduced renal or liver function or jaundice. Isolated cases of angina, ECG abnormalities and rarely, myocardial infarction have been reported following administration of Fluorouracil. Care should be therefore be exercised in treating patients who experience chest pain during courses of treatment, or patients with a history of heart disease.
There have been reports of increased toxicity in patients who have reduced activity/deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD).

Interaction with other medicinal products and other forms of interaction#

Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of Fluorouracil, common drugs include Methotrexate, Metronidazole, Leucovorin as well as Allopurinol and Cimetidine which can affect the availability of the active drug.
Marked elevations of prothrombin time and INR have been reported in a few patients stabilised on warfarin therapy following initiation of fluorouracil regimes.
A clinically significant interaction between the antiviral sorivudine and fluorouracil prodrugs, resulting from inhibition of dihydropyrimidine dehydrogenase by sorivudine or chemically related analogues. Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity

Undesirable effects
Diarrhoea, nausea and vomiting are observed quite commonly during therapy and may be treated symptomatically. An anti-emetic may be given for nausea and vomiting.
Alopecia may be seen in a substantial number of cases, particularly females, but is reversible.
Other side effects include dermatitis, pigmentation, changes in nails, ataxia and fever.
There have been reports of chest pain, tachycardia, breathlessness and E.C.G. changes after administration of Fluorouracil. Special attention is advisable in treating patients with a history of heart disease or those who develop chest pain during treatment.
Leucopenia is common and the precautions described above should be followed.
Systemic fluorouracil treatment has been associated with various types of ocular toxicity.
A transient reversible cerebellar syndrome has been reported following fluorouracil treatment.
Rarely, a reversible confusional state may occur. Cases of leucoencephalopathy have also been reported.
Additionally several other reports have been noted including:
Incidences of excessive lacrimation dacryostenosis, visual changes and photophobia.
Palmar-Plantar Erythrodysesthesia Syndrome has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil.

Thrombophlebitis / Vein Tracking.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. After intracellular conversion to the active deoxynucleotide, it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Flourouracil may also interfere with RNA synthesis.

Pharmacokinetic properties

After intravenous administration, Flourouracil is distributed through the body water and disappears from the blood within 3 hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil ready enters the C.S.F and brain tissue.
Following IV administration, the plasma elimination half-life averages about 16 minutes and is dose dependant. Following a single intravenous dose of Fluorouracil approximately 15% of the

dose is excreted unchanged in the urine within 6 hours; over 90% of this is excreted in the first hour. The remainder is mostly metabolised in the liver by the usual body mechanisms for uracil.

PHARMACEUTICAL PARTICULARS

List of excipients
Sodium Hydroxide
Water for Injections

Incompatibilities

Fluorouracil is incompatible with Carboplatin, Cisplatin, Cytarabine, Diazepam, Doxorubicin, other Anthracyclines and possibly Methotrexate.
Formulated solutions are alkaline and it is recommended that admixture with acidic drugs or preparations should be avoided

Shelf life
Before use: 18 months for 2.5 g/50 ml and 1 g/20 ml Onco-Vial® presentation,
24 months for all other presentations.
In use: Chemical and physical in-use stability has been demonstrated for 5 days at 20-21°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage
Do not store above 25°C. Do not refrigerate or freeze. Keep container in the outer carton
The pH of fluorouracil injection is 8.9 and the drug has maximal stability over the pH range 8.6 to 9.0.
If a precipitate has formed as a result of exposure to low temperatures, redissolve by heating to 60°C accompanied by vigorous shaking. Allow to cool to body temperature prior to use.
The product should be discarded if it appears brown or dark yellow in solution.

Instructions for use, handling and disposal
Cytotoxic Handling Guidelines
Should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.
Fluorouracil Injection should only be prepared for administration by professionals who have been trained in the safe use of the preparation. Preparation should only be carried out in an aseptic cabinet or suite dedicated for the assembly of cytotoxics.
In the event of spillage, operators should put on gloves, face mask, eye protection and disposable apron and mop up the spilled material with a absorbent material kept in the area for that purpose. The area should then be cleaned and all contaminated material transferred to a cytotoxic spillage bag or bin and sealed for incineration.

Contamination

Fluorouracil is an irritant, contact with skin and mucous membranes should be avoided.

In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of the skin. Medical advice should be sought if the eyes are affected or if the preparation is inhaled or ingested.
Please refer to company for COSHH hazard datasheets.

Disposal

Syringes, Onco•Vials® and adaptors containing remaining solution, absorbent materials, and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated at 700°C.

Diluents

Fluorouracil Injection may be diluted with Glucose 5% Injection or Sodium Chloride 0.9%

Appendix 1

NCI Common Toxicity Grading Criteria

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WCC	>4	3.0-3.9	2.0-2.9	1.0-1.9	<1
Plats	Normal	75-Normal	50-75	25-50	<25
Hb	Normal	10-Normal	8-10	6.5-7.9	<6.5
Granulocytes	>2	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Lymphocytes	>2	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Haemorrhage	none	mild, no transfusion	gross 1-2 units transfusion/ episode	gross 3-4 units transfusion/ episode	massive >4 units transfusion/ episode
Infection	none	mild	moderate	severe	life threatening
Nausea	none	mild, able to eat reasonable intake	intake significantly reduced	no significant intake	
Vomiting	none	1 episode /24hs	2-5 episodes /24hs	6-10 episodes /24hs	>10episodes/24s or requiring parenteral support
Diarrhoea	none	increase of 2-3 stools per day over pre Tx	increase of 4-6 stools per day nocturnal stool or moderate cramping	increase of 7-9 stools per day, incontinence or severe cramping	increase of >10 stools per day, grossly bloody stool or parenteral support
Stomatitis	none	painless ulcer or mild soreness	painful erythema, oedema or ulcers but can eat	painful erythema oedema or ulcers and cannot eat	requires parenteral or enteral support
Bilirubin	Normal		<1.5 x N	1.5-3.0 x N	>3.0 x N
Transaminase	Normal	<2.5 x N	2.5-5 x N	5 - 20 x N	>20 x N
Alk Phos	Normal	<2.5 x N	2.5-5 x N	5 - 20 x N	>20 x N
Liver-Clinical	no change			pre coma	coma
Creatinine	Normal	<1.5 x N	1.5-3.0 x N	3.1-6 x N	>6 x N
Proteinuria	no change	1+ or <0.3g% or <3g/l	2-3+ or <0.3-1g% or 3-10g/l	4+ or >1.0g% or <10g/l/l	nephrotic syndrome
Heamaturia	negative	micro only	gross/no clots	gross +clots	requires transfusion
Alopecia	no loss	mild hair loss	pronounced or total hair loss		
Pulmonary	no change	asymptomatic abnormality in pulmonary function tests	dyspnoea on exertion	dyspnoea on normal activity	dyspnoea at rest
Cardiac	none	asymptomatic	recurrent or	requires	hypotension,

Arrhythmias			persistent, no therapy required	treatment	ventricular tachycardia or fibrillation
Cardiac Function	none	asymptomatic decline of resting ejection fraction by <20% of base line value	asymptomatic decline of resting ejection fraction by >20% of base line value	mild CHF responsive to therapy	severe or refractory CHF
Cardiac - ischaemia	none	non-specific T wave flattening	asymptomatic ST ot T wave change suggesting ischaemia	angina without evidence of myocardial infarction	acute myocardial infarction
Cardiac - pericardial	none	asymptomatic effusion no therapy required	pericarditis	symptomatic effusion drainage required	tamponade, drainage urgently required
Hypertension	no change	asymptomatic transient increase by greater that 20mmHg or to >150/100 if previously normal-no treatment required	recurrent or persistent increase by greater that 20mmHg or to >150/100 if previously normal-no treatment required	requires therapy	hypertensive crisis
Hypotension	no change	changes requiring no therapy including transient orthostatic hypotension	requires fluid replacement or other therapy but not hospitalisation	requires therapy and hospitalisation resolves within 48hrs of stopping the agent	requires therapy and hospitalisation for > 48hrs after stopping the agent
Neurosensory	no change	mild paresthesia loss of deep tendon reflexes	mild or moderate objective sensory loss, moderate paresthesia	severe objective sensory loss or paresthesia that interferes with function	
Neuromotor	no change	patient weakness, no objective findings	mild objective weakness without significant impairment of function	objective weakness with significant impairment of function	paralysis
Neurocortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence or agitation, confusion, disorientation	coma, seizures, toxic psychosis

				hallucinations	
Neuocerebellar	none	slight un-coordination dysdiadokinesis	intension tremor, dysmetria, nystagmus	locomotor ataxia	cerebellar necrosis
Mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal intension
Headache	none	mild	moderate or severe but transient	unrelenting and severe	
Constipation	none	mild	moderate	severe	ileus
Hearing	none	asymptomatic, on audiometry only	tinitus	loss interfering with function correctable with hearing aid	incorrectable deafness
Vision	no change			symptomatic subtotal loss of vision	blindness
Skin	none	asymptomatic scattered rash	scattered rash with pruritis or other symptoms	generalised symptomatic erruption	exfoliative or ulcerative dermatitis
Allergy	none	transient rash, drug fever <38C	urticaria, drug fever =38C, mild bronchospasm	serum sickness bronchospasm requires parental med	anaphylaxis
Fever-absence of infection	none	37.1-38C	38.1-40C	>40C for less than 24hs	>40C for more than 24hs
Wt gain or loss	<5%	5-9.9%	10-19.9%	>20%	
Hyperglycaemia mg/dl	<116	116-175	161-250	251-500	>500 or ketoacidosis
Amylase	normal	1.5 x N	1.5-2.0 x N	2.1-5 x N	5.1 x N
Hypercalcaemia	<10.6	10.6-11.5	11.6-12.5	12.6-13.4	>13.5
Hypocalcaemia mg/dl	>8.4	8.4-7.8	7.7-7.0	6.9-6.1	<6.0
Hypomagnesaemia mg/dl	>1.4	1.4-1.2	1.1-0.9	0.8-0.6	<0.5
Fibrinogen	normal	.99-0.76 X control	0.75-0.5 X control	0.49-0.25 X control	<0.24 X control
Prothrombin Time	normal	1.01-1.25X control	1.26-1.5 X control	1.51-2.0 X control	>2.00X control
Partial Thromboplastin time	normal	1.01-1.66X control	1.67-2.33X control	2.34-3.00 X control	>3.00X control

Appendix 2

Definition of Adverse Events

SAEs must be reported to the Sponsor with 24 hours of becoming aware of the occurrence.

It will be the Sponsor's responsibility to inform the Competent Authority (MHRA) and the main REC.

Adverse Event:
Any untoward medical occurrence in a patient administered TPF and which does not necessarily have to have a causal relationship with the treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medical product.

Pre-existing conditions that worsen during a study are to be reported as adverse events. They become serious adverse events if they fulfil one of the seriousness criteria described below.

Serious Adverse Events:

Any event that at any dose fulfils at least one of the following criteria:

is fatal (results in death) (note: death is an outcome, not an event)

is life-threatening (note: the term "life threatening" refers to an event in which the patient was at risk of death at the time of he event; it does not refer to an event which could hypothetically have caused death had it been more severe)

required inpatient hospitalisation or prolongation of existing hospitalisation (note: "inpatient hospitalisation" refers to unplanned overnight hospitalisation).

results in persistent or significant disability/incapacity

is a congenital anomaly/birth defect.

is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Pregnancy.

An adverse event that is considered serious must be reported within one working day (IMMEDIATELY) by the investigator. It is a legal requirement to report serious adverse events. All serious adverse events must also be reported on the Adverse Event page of the case report form.

It is important that the severity of an adverse event is not confounded with the seriousness of the event. For example, vomiting that persists for many hours may be severe, but is not necessarily a serious adverse event. On the other hand, a mild stroke that results in only a limited degree of disability may be considered a serious adverse event.

Expectedness

An unexpected adverse event is one, the nature or severity of which is not consistent with the applicable product information.

Causality - see appendix 3

Treatment and Follow-Up of Adverse Events

All adverse events must be documented and followed up until the event is either resolved or adequately explained, even after the subject has completed the trial treatment.

Appendix 3

Adverse Events Categories for Determining Relationship to Test Drug

Probable (must have first 3)

This category applies to those adverse events that are considered, with a high degree of certainty, to be related to the test drug. An adverse event may be considered probable if:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It disappears or decreases on cessation or reduction in dose. (There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g. (1) bone marrow depression, (2) tardive dyskinesia).
4. It follows a known pattern of response to the suspected drug.
5. It reappears upon re-challenge.

Possible (must have first two)

This category applies to those adverse events in which the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered possible if, or when:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It may have been produced by the subject's clinical state, environment or toxic factors, or other modes of therapy administered to the subject.
3. It follows a known pattern of response to the suspected drug.

Remote (must have the first two)

In general this category is applicable to an adverse event which meets the following criteria:

1. It does **not** follow a reasonable temporal sequence from administration of the drug.
2. It may have been produced by the subject's clinical state, environment or toxic factors, or other modes of therapy administered to the subject.
3. It does **not** follow a known pattern of response to the suspected drug.
4. It does not reappear or worsen when the drug is re-administered.

Unrelated

This category is applicable to those adverse events that are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc) and do not meet the criteria for drug relationship listed under "**Remote, Possible, or Probable**".

Appendix 4

Eastern Co-operative Oncology Group (ECOG)

Performance Status Scale

ECOG Scale	Performance status
0	Fully active, able to carry out all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Out of bed more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead

Appendix 5
Patient Information Sheet

Taxotere in Palliative Therapy: A Pilot study of Taxotere (Docetaxel) , Cisplatin and 5FU (T.P.F.) in the palliative treatment of squamous cell carcinoma of the head and neck.

Before you decide on participating in this clinical trial, we would like to explain to you why we consider this research project as important and what it involves. Please take time to read the following information carefully and discuss it with friends, relatives and your doctor, if you wish. Ask your doctor, if there is anything not clear and if you would like to have more information. Take your time to decide whether or not you would like to participate in this study. This study is a clinician - initiated and clinician led study, organized and run by the Royal Wolverhampton Hospitals NHS trust who is also the sponsor of the study. The running costs of the study are met through a research grant provided by Sanofi-Aventis. Your doctor will not receive any personal financial payment for including you in this trial.

Why have I been asked for the study?

We have decided to ask you to participate in this study, because you have the type of cancer that may benefit from the therapy under investigation..

Introduction

Your doctor will have told you that you have cancer of the head and neck that cannot be treated with radiotherapy (X-ray treatment) or surgery. We would like to invite you to participate in a clinical research study that investigates the use of a new anti-cancer drug regime called TPF in the treatment of recurrent/advanced cancer of the head and neck.

Purpose of the study

The main aim of this research is to find out the effectiveness of TPF against head and neck cancer. This study is what is known as a phase 2 study . In this type of study we wish to formally investigate the effectiveness of a new treatment to see if it would be suitable for assessment in a larger study where the treatment would be compared against the current standard treatment. This type of study is also known as a pilot study. If the study shows this treatment is safe it will be used in a multicentre national study to further evaluate the effectiveness of the treatment against the current standard treatment.

Treatment for head and neck cancer

The usual treatment for head and neck cancer is radiotherapy or surgery. In some cases though head and neck cancer is either too advanced, or fails to respond to treatment. In this case chemotherapy may be given to relieve symptoms, however the results can be disappointing.

A drug regime called Cisplatin and 5FU (PF) has been used with some success. Recently a new drug Taxotere (Docetaxel) has been used in head and neck cancer in combination with Cisplatin and 5FU (TPF) before patients have had potentially curative surgery and has been shown to be more effective than Cisplatin and 5FU alone in this situation. This study aims to confirm the effectiveness of TPF in the treatment of head and neck cancer if the cancer returns after surgery or radiotherapy.

What will happen to you?

If you agree to take part, you will be assessed for treatment in the usual way.Within the 4 weeks preceding the study your doctor will ask you questions about your health and give you a full physical

examination including your temperature, heart rate, blood pressure, weight and height. Your doctor will also ask you what kind tablets you are taking and what kind of treatment you have had for your cancer in the past. You will be asked for a blood sample and your height and weight will be taken. A scan (CT or MRI) may be required so your doctor can monitor the effect ot the treatment on the cancer. If your doctor can measure your tumour by examining you alone, then you will not need a scan. If a CT or an MRI scan is need to measure your tumour then this will be repeated after every 3 courses of chemotherapy. If you are a woman of child bearing age we will need to perform at test to ensure you are not pregnant before starting any treatment.

The chemotherapy is given by injection through a drip over 5 days on a 21 day cycle. The effect of the treatment on your cancer will be assessed after every three courses. Treatment may be given either as an inpatient where you will be admitted to hospital for the duration of the treatment , or as an outpatient. If treatment is to be given as an outpatient we will need to arrange for what is known as a Hickman line to be inserted. A Hickman line is flexible plastic cannula (drip line) which is placed in to one of the large veins which runs under you collar bone . The line will be put in under local anaesthetic. The line will stay in place throughout the course of your treatment.. Outpatient treatment may not be suitable for everyone, so your doctor will discuss which of these options may be the most appropriate approach with you.
A maximum of six courses will be given and your doctor will monitor your progress prior to each dose of chemotherapy. Prior to each course of chemotherapy your doctor will examine you and ask questions about any symptoms or problems you may have had. Once you have completed all your treatment you will be still seen regularly at the hospital clinic for check-ups .
You will also be asked to complete a simple questionnaire which will help us to evaluate the effects of the treatment on you r quality of life at the beginning and end of your treatment, and again at intervals after your treatment when you come for routine check-ups.

What are the risks?

TPF can cause lowering of the blood count, which can lead to an increased risk of infection. Your blood count will be monitored during treatment. Also you will be routinely given antibiotics to help prevent infection. It will still be necessary for you to monitor your temperature twice a day during chemotherapy and contact us urgently if you either develop a fever or feel unwell at any time.

Other potential side effects include a reduction in kidney function, a sore mouth and diarrhoea but these side effects also may occur with standard Cisplatin and 5FU chemotherapy.

How will you benefit?

You may not benefit from taking part in this study. Although there are good reasons for thinking that TPF may be more effective than our standard treatments we have no proof that this is the case. Indeed, you may experience increased side effects if you receive this treatment. We can never promise a benefit from a new treatment before it is fully tested but your participation will increase our understanding of the use of TPF in this setting and could lead to improved treatment for future patients in your position. If TPF does represent a more effective treatment than current treatments you yourself may benefit.

Do you have to say yes?

Participation in this study is voluntary. You can decline to take part or withdraw from the study at any time without giving a reason. This will mean that you will receive the standard treatment of

Cisplatin and 5FU chemotherapy and your care will not be affected now or in the future. Your doctor may also withdraw you from the study if he/she thinks it is in your best interest.

What do I have to do?
It is important that you inform your research doctor of any change in your health whether or not you think that it is related to the study medication. You must tell your doctor about any change in your medication, both medication that has been prescribed by your (family) doctor and medication which you can obtain without prescription from your pharmacy, chemist or organic food store. You should ask your doctor before taking any new medication and always comply with your doctor's instructions during the study. For safety reasons, pregnant woman should not participate in this clinical trial. Only woman who can no longer become pregnant, i.e. who are postmenopausal or practice a medically accepted contraception method, may participate in this trial. Male patients wishing to participate have to make sure not to father a child while being in the study (e.g. by using adequate contraception).

What if new information becomes available?
Sometimes during a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in this study. If you decide to withdraw from the study, your doctor will make arrangements for your care to be continued. If you decide to go on with the study, you will be asked to sign an updated consent form. On the basis of new information that may arise during the time that this study is conducted, your research doctor may consider it is in your best interest to withdraw you from the study. He/she will explain the reasons for this to you and arrange for your care to be continued.

What happens when the research study stops?
Your doctor will discuss with you the possible treatments available after the end of the study. It is possible that the study may be terminated prematurely . If this happens, your doctor will explain the reasons to you.

Patient Confidentiality

All the information collected about you during the course of the research will be kept strictly confidential. You will only be identified in study records by your initials and special study number, any information about you that leaves the hospital will have your name and address removed from it so you cannot be recognised from it. Occasionally we may need to check your medical records to make sure the information provided about you is accurate. This will be done by clinical staff or the sponsors personnel. A government body called the Medicines and Healthcare Products Regulatory Agency (MHRA) may also require access to your medical records to ensure the study is being ran in accordance with UK law. Your medical records will be kept confidential and stored by the hospital for 15 years. Your GP will be informed that you are participating in this study.

Who has reviewed the Trial

This trial has been reviewed and scientifically approved by Sanofi-Aventis Global research committee and by the national committee representing the Head and Neck national clinical research network. It has received authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA), National and Local Ethics Committee and the participating hospitals Research and Development office.

For further information regarding this study please contact:

Chief Investigator :- Dr Caroline Brammer, New Cross Hospital , Wolverhampton, WV10 0QP. Tel 01902695201

Study site coordinator :-

Appendix 6

Written Consent Form

Taxotere in Palliative Therapy: A Pilot study of Taxotere (Docetaxel) Cisplatin and 5FU in the palliative treatment of squamous cell carcinoma of the head and neck.

Protocol Version
Patient Identification Number:
Name of Researcher:

Patient please initial box

1. I confirm that I have read and understood the information sheet version…….. for the above study. ☐
2. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities or the Trust, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records and for the data to be transferred to them. ☐
5. I agree that my GP can be informed of my participation in this study. ☐
6. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

Each individual who signs this document must PERSONALLY date his or her signature.

1 for patient, 1 for researcher, 1 to be kept with hospital notes.

Appendix 7
Letter to GP

date

Dear Dr

Your patient has agreed to participate in a clinical study investigating the addition of Taxotere (Docetaxel) to traditional cisplatin and 5FU chemotherapy in the palliative treatment of head and neck cancer. Expected side effects from this drug include diarrhoea, nausea and vomiting, stomatitis and neutropenia. Other common side effects are fatigue and anorexia. Your patient will be reviewed routinely every 3 weeks during the study by the supervising oncologist. Please contact at should you require any further information or advice regarding your patient's management.

Thank you.

Yours sincerely,

Appendix 8

Clinical Record Form

T.In Pa.T. Registration

Date of Form Completion _____

Patient initials _____

Hospital Record Number _____

Treating Centre _____

Inclusions

Histologically proven squamous carcinoma the head and neck, excluding carcinoma of the nasopharynx	**Yes**	**No**
Patients must have disease that is considered unsuitable for radical treatment with either surgery or radiotherapy. Either, or both forms of treatment may have been used previously in patients who have progressive disease but measurable disease recurrence must be present outside of a previously irradiated area if radiotherapy was completed within 6 months of randomisation.	**Yes**	**No**
Patients must be considered fit for chemotherapy.	**Yes**	**No**
ECOG performance status of 0,1 or 2.(appendix 7)	**Yes**	**No**
Able and willing to give written informed consent and to comply with the protocol for the duration of treatment and follow up.	**Yes**	**No**
Expected survival greater than 3 months from entry into study	**Yes**	**No**

Adequate renal function **Yes** **No**

Exclusions

Women who are lactating or pregnant **Yes** **No**

Patients who have received previous chemotherapy for malignant disease or cytotoxic chemotherapy within 6 months prior to treatment, radiotherapy within 6 weeks or if they have ongoing acute radiotherapy toxicity. **Yes** **No**

Patients who have received radiotherapy within 6 weeks or if they have ongoing acute radiotherapy toxicity. **Yes** **No**

A history of nervous or psychiatric disorder that would preclude informed consent or compliance with oral drug intake or treatment **Yes** **No**

A history of previous malignancy within the previous 5 years except successfully treated basal cell cancer of skin or carcinoma in situ of cervix. **Yes** **No**

Patients with the following laboratory values **Yes** **No**

1. Hb<10g/dl that cannot be corrected by blood transfusion.
2. Neutrophil count<1.5x 109/L
3. Platelets<100x109/L
4. Serum bilirubin >1.5xULN
5. ALT and/or AST>2.5xULN
6. Alkaline phosphatase>2.5xULN

Patients with uncontrolled infection. **Yes** **No**

Patients with a history of severe hypersensitivity reactions to Docetaxal **Yes** **No**

Completed By _____

Signature _____

Date

Appendix 9

T.In Pa.T. Clinical Record Form

Study Entry

Date of Form Completion _____

Patient initials _____

Hospital Record Number _____

Treating Centre _____

Date of Registration into Study _____

Date of Birth _____

Sex

Height _____

Weight _____

Disease Details

Date of Diagnosis _____

Site _____

Stage at Presentation(TNM) _____

Site of Marker Lesion (s)

1.
2.
3.

Size of Marker Lesion (s)

1.
2.
3.

Previous Treatment

Radiotherapy **Yes** **No**

If Yes

Dose _____
Number of Fractions _____
Overall Treatment Time _____
Date of First Treatment _____

Chemotherapy **Yes** **No**

If Yes

Neoadjuvant **Yes** **No**

Regime (Drugs , Doses, Days if delivery, length of treatment cycle)

_____

Number of Courses _____

Date of First Treatment _____

Concomitant **Yes** **No**

Regime (Drugs , Doses, Days if delivery, length of treatment cycle)

_____

Number of Courses _____

Date of First Treatment _____

Past Medical History

Comorbid conditions

1.
2.
3.
4.
5.

Concomitant Medication

1.
2.
3.
4.
5.
6.
7.

Allergies

On Examination

ECOG

CVS

RS

Abdomen

CNS

Investigations

(From less than 1 week prior to registration)

FBC

Hb= **WCC=** **Neutrophils =** **Platlet count =**

U+E

Na^+ = **K^+ =** **Ur =** **Creatinine=** **Ca^{2+}=**

Cockcroft Gault GFR estimation =

LFT
Bil = **ALT=** **Alk Phos=** **Albumin=**

Completed By _____

Signature _____

Date

Appendix 10

T.In Pa.T. **Clinical Record Form**

On Treatment - To be completed on Day 1 TPF Cycle

Date of Form Completion _____

CYCLE NO _____

Patient initials _____

Hospital Record Number _____

Treating Centre _____

Date of Form Completion _____

First Day of Cycle (Date) _____

Disease Assessment

Size of Marker Lesion (s)

1.
2.
3.

Response

CR PR SD DP

Toxicity

Maximum CTC Grade during the last chemotherapy cycle
∗ insert date of investigation

Nausea _____

Vomiting _____

Diarrhoea _____

Constipation _____

Mucositis _____

Anaemia∗ _____

Neutropenia∗ _____

Thrombocytopenia∗ _____

Alopecia _____

Renal Dysfunction _____

Hepatic Dysfunction _____

Peripheral Neuropathy _____

Fatigue _____

Infection _____

Other 1 _____

Other 2 _____

Continuation Of Therapy

Continue Therapy

Yes No (please complete study withdrawal form if less than 2 cycles given)

Dose Reduction for Next Cycle

Yes No

Date of Day 1 Next Cycle _____

Completed By _____

Signature _____
Date

Appendix 11

T.In Pa.T. **Clinical Record Form**

Follow up

Date of Form Completion _____

Patient initials _____

Hospital Record Number _____

Treating Centre _____

Disease Assessment

Size of Marker Lesion (s)

1.
2.
3.

Evidence of Disease Progression Yes No

Patient Alive Yes No

If No Date of Death _____

Cause of Death _____

Completed By _____

Signature _____

Date

Appendix 12

Clinical Record Form

Study Withdrawal

Date of Form Completion _____

Patient initials _____

Hospital Record Number _____

Treating Centre _____

Date of Withdrawal (or date of death if death on treatment)

_____

Reason for Withdrawal

Disease Progression

Patient Preference

Death on Treatment

Toxicity of Therapy

If withdrawal is for reasons due to toxicity of therapy please give details below

Completed By _____

Signature _____

Date

Appendix 13
SAE Report Form fax to 01902 695624

A Pilot study of Taxotere (Docetaxel) Cisplatin and 5FU in the palliative treatment of squamous cell carcinoma of the head and neck: SAE REPORT FORM.

SAEs must be faxed within 24 hours

Please write clearly in BLACK ink and in BLOCK CAPITALS

Study No.						Randomisation date		Patient No.	Country UK
Patient Initials			Date of Birth			Age	Sex	Height (cm)	Weight (kg)
first	mid	last	day	Month	year		☐ male ☐ female		

Criteria for expedited reporting (tick all applicable)

Seriousness criteria:
- ☐ was life threatening
- ☐ required or prolonged inpatient hospitalization
- ☐ was persistently or significantly disabling/incapacitating
- ☐ is a congenital anomaly
- ☐ resulted in death
- ☐ is medically important

Did the patient take a **significant overdose?** ☐ No ☐ Yes

Date and type of report

Date of THIS report |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)

Date reported to study staff |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)

Report type: ☐ initial ☐ follow up

For follow-up report, give only changes to previous

Was this serious adverse event first reported as a non-serious adverse event? ☐ No ☐ Yes

IF YES, Date event became serious |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)

If event started BEFORE first dose of study medication

Did this event continue and worsen in intensity (severity and/or frequency) after the first dose of study medication? ☐ No ☐ Yes

Description of adverse event and duration

Diagnosis/syndrome of AE

_____

Component signs or symptoms (only if applicable) 1. _____ 2. _____
3. _____ 4. _____ 5. _____

Start of adverse event |__|__| |__|__| |__|__|__|__| (day) / (month) / (year) End of adverse event |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)

Duration if adverse event lasted less than 24 hours: |__|__|__| |__|__| |__|__| (hours) / (minutes) / (sec)

Time since last dose of study medication |__|__|__| |__|__| (hours) / (minutes)

Comments on adverse event:

_____

_____

_____ This section continued on next page

Study No :	Patient No.

A phase II study of Taxotere (Docetaxel) Cisplatin and 5FU in the palliative treatment of squamous cell carcinoma of the head and neck: SAE REPORT FORM

Comments continued _____

_____

_____

_____

_____

Remedial measures

Study medication (select one)

- ☐ no change
- ☐ dosage increased due to event
- ☐ dosage decreased due to event
- ☐ discontinued and reintroduced, no event recurred
- ☐ discontinued and reintroduced, same event recurred
- ☐ discontinued and reintroduced, different event occurred
- ☐ discontinued due to event and subject withdrawn
- ☐ permanently discontinued for other reason
- ☐ other, *please specify* _____

_____

Were there other countermeasures? ☐ No ☐ Yes

***If YES,* Medication** ☐ No ☐ Yes

Other *(please specify)* _____

_____

Causal relationship

Is there a reasonable possibility that the adverse event is associated with the study medication?

☐ No ☐ Yes

*Whether **NO** or **YES**, an alternative explanation may be ticked and details given below:*

- ☐ underlying/concomitant illness
- ☐ possibly associated with concomitant drug(s)
- ☐ directly related to study procedures
- ☐ other known or suspected cause *(please comment)*

_____

_____

_____

Intensity		**Outcome**		
	☐ mild ☐ moderate ☐ severe		☐ recovery without sequelae ☐ ongoing at time of report ☐ subject died	☐ recovery with sequelae ☐ event not resolved, follow-up not deemed necessary by investigator

Relevant medical history (e.g. previous diseases, surgery, allergies, pregnancy)

_____

_____

_____

_____

_____

_____

Study medication: _____

(1) ☐ study medication (2) ☐ active comparator

(3) ☐ placebo (4) ☐ code not broken

Date started |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

Indication _____

Date ended |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

Daily dose _____ Unit _____ Route _____ Batch No. _____

Study No :	**Patient No.**

A phase II study of Taxotere (Docetaxel) Cisplatin and 5FU in the palliative treatment of squamous cell carcinoma of the head and neck: SAE REPORT FORM.

Study medication: _____ (1) ☐ study medication (2) ☐ active comparator (3) ☐ placebo (4) ☐ code not broken

Date started |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)

Indication _____

Date ended |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)

Daily dose _____ Unit _____ Route _____ Batch No. _____

Concomitant medication

List those given at time of event – those given to treat adverse event should be listed under 'Comments' on page 1/2.

Drug	Daily dose	Unit	Route	Indication	Date started day / month / year	Date stopped day / month / year	Ongoing No Yes	*Causal relationship No Yes
[1]								
[2]								
[3]								
[4]								
[5]								
[6]								
[7]								

**Is there a reasonable possibility that the adverse event is associated with the concomitant medication?*

In case of death

Date of death |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)	Was an autopsy performed? ☐ No ☐ Yes ☐ planned *If YES, please provide a copy of the autopsy report*
Was the death related to the study medication?	☐ No ☐ Direct consequence ☐ Indirect consequence

Cause of death *(tick all applicable)*

	No	Yes
Disease for which subject was enrolled into study	☐	☐
Other pre-existing condition(s)	☐	☐
Serious adverse event	☐	☐
Unknown	☐	☐

(*Further information will be requested)*

Cause(s) of death ranked in order of likelihood

1. _____
2. _____
3. _____
4. _____

Study No :	**Patient No.**

Investigator Name and address:	**Investigator** Date (day/month/year): Signature:

Appendix 14

Schedule of Events

	Baseline[a]	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**End of treatment** (6 weeks after start of last cycle)	**Follow up** every 6 weeks for 6 months then 3 monthly until progression
Informed Consent	x								
History	x								
Concomitant Medications	x								
Physical examination	x	x	x	x	x	x	x	x	x
Site and stage of disease	x	x	x	x	x	x	x	x	x
Height, Weight	x							x	x
Body Surface Area	x								
Full Blood count	x	x	x	x	x	x	x		
Clinical Chemistry[b]	x	x	x	x	x	x	x		
Creatinine Clearance[c]	x	x	x	x	x	x	x		
CT scan	x			X end of cycle			X end of cycle		As clinically indicated
Chemotherapy treatment		x	x	x	x	x	x		
Toxicity		x	x	x	x	x	x	x	x
Adverse Events		x	x	x	x	x	x		
EORTC QLQ -30 and H+N 35	x							x	x

a Baseline: All to be carried out prior to registration and randomisation and within 2 weeks prior to the start of treatment, except CT scan/ MRI which can be done up to 6 weeks prior to the start of treatment

b Biochemistry to include: Urea, creatinine and electrolytes, LFTs.

c Creatinine Clearance by the Cockroft and Gault calculation

NOTE Patients will be followed regularly until death or end of trial. Follow-up after 6 months will be 3 monthly until progression. After Progression follow up will be as clinical need dictates, with additional cancer treatments and death to be reported on the appropriate CRF supplied in investigator folder

Appendix 2

References

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2.Head and Neck cancer. Vokes et al ; NEJM, 328: 184-194,1993.
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4.Dibromodulcitol plus bleomycin compared with bleomycin alone in head and neck cancer: Cancer Chemotherapy and Pharmacology. Issel et al; ,8(2):161-3,1982.
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8. A Randomised Study Comparing Neoadjuvant Taxotere (Docetaxel) Plus Cisplatin Plus 5-Florouracil Versus Neoadjuvant Cisplatin Plus 5- Florouracil In Patients With Locally Advanced Unresectable Squamous Cell Carcinoma Of The Head And Neck. (EORTC 24791) Vermorken et al; Proc. Am. Soc. Clin. Oncol, 2004..
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Appendix 3

Re: TInPaT Amendments to Protocol Version 11

a) Amendment 1 Page 6 version 11

> ***2.1 Primary Objectives***
> *To determine the response rate (CR plus PR) and tolerability of Taxotere (Docetaxel) 75mg/m2 over 1 hr i.v. Day 1 plus Cisplatin i.v75mg/m2 Day 1 over 2hrs plus 5FU 750 mg/m2 i.v. over 24hrs Day 1-4 (TPF) for the palliative treatment of squamous cell carcinoma of the head and neck.*
> and page 11 version 11
> ***7. Study medication***
> ***Day 1***
> *Taxotere (Docetaxel) 75mg/m2 over 1 hr i.v.*
>
> *N. Saline 1 lire over 2 hr*
>
> *Manitol 20% 100mls over 15minutes*
>
> *Cisplatin i.v.75mg/m2 Day 1 over 2hrs*
>
> *N.Saline 1 litre over 2 hr plus Mg SO4 1g*
>
> *plus*
>
> ***Day 2-5***
>
> *5FU 750 mg/m2 i.v. over 24hrs (may be given as an outpatient via Hickman line and syringe driver)*
>
> *Plus Augmentin 625mg t.d.s. Days 7-16or Ciprofloxacin 500mg b.d. days 7-16*
>
> *Plus G-CSF (Granocyte,Lenograstim) days 4-11*

To be amended to

> ***2.1 Primary Objectives***
> *To determine the response rate (CR plus PR) and tolerability of Taxotere (Docetaxel) 60mg/m2 over 1 hr i.v. Day 1 plus Cisplatin i.v60mg/m2 Day 1 over 2hrs plus 5FU 600mg/m2 i.v. over 24hrs Day 1-4 (TPF) for the palliative treatment of squamous cell carcinoma of the head and neck.*
>
> ***7. Study medication***
> ***Day 1***
> *Taxotere (Docetaxel) 60 mg/m2 over 1 hr i.v.*
>
> *N. Saline 1 lire over 2 hr*
>
> *Manitol 20% 100mls over 15minutes*
>
> *Cisplatin i.v.60mg/m2 Day 1 over 2hrs*
>
> *N.Saline 1 litre over 2 hr plus Mg SO4 1g*
>
> *plus*
>
> ***Day 2-5***
>
> *5FU 600 mg/m2 i.v. over 24hrs (may be given as an outpatient via Hickman line and syringe driver)*
>
> *Plus Augmentin 625mg t.d.s. Days 7-16or Ciprofloxacin 500mg b.d. days 7-16*
>
> *Plus G-CSF (Granocyte,Lenograstim) days 4-11*

Amendment 1 is required as all 3 of the first 3 patients entered in to the study have required dose reduction after the first course of the treatment and it is my belief that it would not be in the patients best interest to continue with the study at current dose levels

b) Amendment 2 page 8 version 11

5.1 Assessments
Please see table in appendix 14.
Clinical assessment of the patient will be taken prior to each cycle, radiological assessments if required every 3 cycles.

Will be amended to

5.1 Assessments
Please see table in appendix 14.
Clinical assessment of the patient will be taken within 3 days of day 1 of the next cycle, radiological assessments if required every 3 cycles.

c) Amendment 3 page 11 version 11

5.5 Quality of Life

The EORTC QLQ 30 and QLQ- H+N35 will be completed by the patient at study entry, at 6 weeks following completion of chemotherapy and every 3 months thereafter.

Will be amended to

5.5 Quality of Life
The EORTC QLQ 30 and QLQ- H+N35 will be completed by the patient at study entry, at 6 weeks +/- 7 days following completion of chemotherapy and every 3 months +/- 14 days thereafter.
.

d) Amendment 4 page 12 version 11

8. Acute Toxicity
Toxicity will be within assessed every 21 days during TPF therapy and at 6 weeks days following completion of chemotherapy . Toxicity will be graded using NCIC Common Toxicity Criteria version 3.

Will be amended to

8. Acute Toxicity
Toxicity will be within 3 days of commencing the next cycle of treatment during TPF therapy and at 6 weeks +/- 14 days following completion of chemotherapy . Toxicity will be graded using NCIC Common Toxicity Criteria version 3.

The amendments 2-4 are required to allow a little more flexibility for assessments as the current protocol is too prescriptive to be practical.

e) Amendment 5

The study will run from April 2009 to April 2010 as the study did not open until April 2009 rather than those detailed in the initial submission to the ethics committee.

Appendix 4 CV Chief Investigator

Name:	
Dr. Caroline Brammer	
Present appointment: *(Job title, department, and organisation.)*	
Consultant Clinical Oncologist, Department of Oncology, Deanesly Centre, The Royal Wolverhampton Hospitals NHS Trust	
Address: *(Full work address.)*	
The Deanesly Centre, The Royal Wolverhampton Hospitals NHS Trust, New Cross Hospital, Wednesfield Road, Wolverhampton. WV10 0QP	
Telephone number:	**Email address:**
01902 695201	caroline.brammer@rwh-tr.nhs.uk

Qualifications:

- Bachelor of Medicine – July 1991
- Bachelor of Surgery – July 1991
- MRCP (UK) Part 1, London – February 1993
- MRCP Part 2, London – June 1994
- FRCR (UK) Part 1, UK – June 1995
- FRCR Part 2, UK– April 1998

Professional registration: *(Name of body, registration number and date of registration.)*

GMC Full Registration Number - 3539091

Previous and other appointments: *(Include previous appointments in the last 5 years and other current appointments.)*

- Specialist Registrar in Clinical Oncology, Cookridge Hospital, Leeds – November 1996 – November 1999
- Registrar in Radiation Oncology, Auckland Hospital, New Zealand – December 1995 – November 1996
- Registrar in Radiotherapy and Clinical Oncology, Leicester Royal Infirmary – October 1994 – October 1995
- Senior House Officer, Respiratory Medicine, Derby City General Hospital – August 1994 – October 1994
- Senior House Officer, Derby City General Hospital – February 1994 – August 1994
- Senior House Officer, Gastroenterology and General Medicine, Derby City General Hospital – August 1993 – January 1994
- Senior House Officer, Intensive Care and Haematology, Derby City General Hospital – February 1993 – July 1993
- Senior House Officer, Department of Medicine for the Elderly, Derby City General Hospital – August 1992 – January 1993
- House Officer, General Surgery, Chesterfield and N Derbyshire Royal Hospital – May 1992 – July 1992
- House Officer, Urology, Chesterfield and N Derbyshire Royal Hospital – February 1992 – April 1992
- House Officer, General Medicine and Hepatology, Royal Hallamshire Hospital, Sheffield – August 1991 – October 1991

Research experience: *(Summary of research experience, including the extent of your involvement. Refer to any specific clinical or research experience relevant to the current application.)*

I am Head and Neck cancer research lead for the Greater Midlands Cancer Research Network.
I am currently recruiting patient for the following studies :, PET-NECK, Persephone, REACT, BIG-DCIS, Fragmatic, COSTAR I have entered patients into many multi-centre randomised trials. eg Trial of Radiation dose for stage 1 Non Hodgkin's Lymphoma ABC, ATAC, Big Lung Trial, CR07, Trial of Radiation dose for stage 1 Non Hodgkin's Lymphoma , SECRAB, START etc. I have been chief investigator for 2 completed local studies and am the UK chief investigator CONCRT 2.

Research training: *(Details of any relevant training in the design or conduct of research, for example in the Clinical Trials Regulations, Good Clinical Practice or other training appropriate to non-clinical research. Give the date of the training.)*

ICH/GCP Training, New Cross Hospital – 2011
QA Training, New Cross Hospital – 18th March, 2009

Relevant publications: *(Give references to all publications in the last two years plus other publications relevant to the current application.)*

1)The Acceptability of Open Access Follow-up Clinics Following Palliative Radiotherapy for Carcinoma of the Bronchus from a Clinician, Community Palliative Care and Patient Viewpoint. J.Adlard J.Joseph C.V. Brammer, G.E.GerrardClinicalOncology13(6):404-8,2001.
2) Primary CD 30 +ve anaplastic large cell lymphoma of the breast presenting in pregnancy. A Lengyel, J Adjogatse, R Mehra, C. Brammer, W Fuggle, E Jones, B Isgar.The Breast 11, 457-459,2002

3)Book Review: Principles and Practice of Brachytherapy using afterloading systems .C.Brammer. Clinical Oncology 2002

4)Early Radiotherapy related morbidity. Hartley A. Giridharan S. Begum G. Billingham L. Brammer C. .Radiotherapy & Oncology. 68(1):89-90, 2003 Jul.

External Beam Radiotherapy in the Management of Differentiated Thyroid Cancer. Ford D, Giridharan s, Mc Conkey C, Brammer C, Watkinson JC, Glaholm J. Clinical Oncology, Sept 2003 Vol 15 (6) 337-342.

5)HIV associated hodgkins disase of th anal canal. S Hikkman, C Brammer. Clinical Oncology 17 (11) p69 , 2005

6)A Case of Hypersensitity Vasculitis after Vinorelbine Injection in a Patient with Metastatic Breast Cancer. D. Bilku, C Brammer . Clinical Oncology vol 19 – 363, 2007

7)Cost-Effectiveness of Docetaxel with Cisplatin/5FU versus standard treatment as induction chemotherapy followed by concurrent chemoradiation therapy in locally advanced squamous cell cancer of the head and neck:Anju Partan, Jeroen Jansen, Chris Evans, Pr Posner, Philippe Beltran, Caroline Brammer. Abstract no 6069 ASCO 2007

8)A Retrospective Comparison of Dose Intensity Between Weekly Cisplatin And 3-weekly Cisplatin Delivered Concurrently with Radical Radiotherapy For Locally Advanced Head and Neck Squamous Cell Carcinoma At New Cross Hospital, Wolverhampton: K.F. Ho, C.V. Brammer . Acta Oncologica 2008 1-6

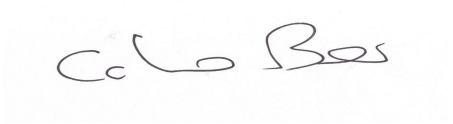
9)Consensus conference: Implementing treatment recommendations on yttrium-90 immunotherapy in clinical practice – Report of a European workshop, 15 January 2008
Pier Luigi Zinzani, Francesco d'Amore, Emilio Bombardieri, Caroline Brammer, José Gómez Codina, Tim Illidge, Wojciech Jurczak, Werner Linkesch, Franck Morschhauser, Elisabeth Vandenberghe, Achiel Van Hoof
European Journal of Cancer Vol44(3) 366-373,2008

10)Partan A, Posner MR, Brammer C , Beltran P, Jensen JP
Cost Utility analysis of doxectaxel as induction chemotherapy followed by chemoirradiation in locally advanced SCC H+N Head & Neck. 31(10):1255-62, 2009 Oct

11) Cetuximab (Erbitux) Plus Radiotherapy (ERT) Versus Concomitant Cisplatin Plus Radiotherapy (CRT) Within An NHS Oncology Unit (New Cross Hospital Wolverhampton. A randomised study: Abstract 22. Oral Presentation. 3rd Trends in Head and Neck Oncology Meeting. 3rd November 2011. Rome

12)Patients receiving concomitant Cisplatin and Radiotherapy require admission and non routine intervention due to acute toxicity more frequently than those receiving Cetuximab and Radiotherapy. Abstract 35 . Poster Presentation 3rd Trends in Head and Neck Oncology Meeting. 3rd November 2011. Rome

13) A Pilot Study Of Taxotere (Docetaxel), Cisplatin, And 5FU (TPF) In The Palliative Treatment Of Squamous Cell Carcinoma Of The Head And Neck. Abstract 33 . Poster Presentation 3rd Trends in Head and Neck Oncology Meeting. 3rd November 2011. Rome

Signature:	**Date:**
	13/01/2012

Appendix 5

See poster attached

A Pilot Study Of Taxotere (Docetaxel), Cisplatin, And 5FU (TPF) In The Palliative Treatment Of Squamous Cell Carcinoma Of The Head And Neck
Author Caroline Brammer. Deanesly Centre, New Cross Hospital, Wolverhampton,

International Trends In Head and Neck Cancer : Rome 3rd November 2011.

Appendix 6

Patient Data Listings

For individual AE data please see page 14 of trial report

For individual response to treatment please see page 13 and 14 of trial report

For individual SAE data please see page 18-20 of trial report

Discontinued Patients

Tin 2 discontinued due to disease progression after 2nd cycle

Tin 4 discontinued after 1 cycle chemotherapy due to life threatening toxicity

Tin 5 discontinued 1 cycle chemotherapy due to life threatening toxicity

Excluded Patients

Tin 7 excluded as the presumed metastatic mediastinal lymphadenopathy remained static after 2 cycles of chemotherapy while the primary site disease resolved significantly. The discordant response led the reporting radiologist to conclude that the mediastinal lymphadenopathy was reactive. The patient was therefore deemed to have potentially curable disease and therefore received neoadjuvant chemotherapy followed by radical chemoradiotherapy and was excluded from the study.

Protocol Deviations

TIN 4 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2 prior to finalization of amendment to reduce doses. This was not considered a serious breach as the amendment had already been proposed. This patient had life threatening toxicity despite the lower doses of chemotherapy being prescribed

TIN 5 Taxotere 60mg/m2, Cisplatin 60mg/m2, 5FU 600mg/m2 prior to finalization of amendment to reduce doses. This was not considered a serious breach as the amendment had already been proposed. This patient had life threatening toxicity despite the lower doses of chemotherapy being prescribed

TIN 7 Regarded to have locally advanced rather that metastatic disease after 2 cycles of chemotherapy. Therefore chemotherapy was continues to 3 cycles with neoadjuvant intent, followed by chemoradiotherapy as is standard therapy for patients with locally advanced inoperable disease.