Concurrent chemoradiotherapy for stage III NSCLC followed by consolidation Pemetrexed: a phase II study

CONCEPT

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CONTENTS

1. **Title and abstract**
   (To be completed by author)

2. Introduction and background

Lung cancer is the leading cause of cancer death in the world. Non small Cell Lung Cancer (NSCLC) accounts for 80-85% of all lung cancers, and one third of patients present with locally advanced (stage III) tumours. The prognosis for patients with stage III NSCLC is heterogeneous because the stage spans IIIA and IIIB disease that includes T3N1; T4 and N; and any T, N2, or N3. Although patients with malignant effusion in the absence of distant metastases fall into the IIIB subcategory their prognosis is as poor as stage IV NSCLC. With the exception of stage IIIB (effusion) tumours for which the management is palliative, treatment is based on whether the disease is resectable, potentially resectable or unresectable. The latter form the majority of cases and despite advances in combined modality treatments the prognosis for these patients is generally poor. Consequently new therapeutic approaches are required to improve outcome and /or reduce the toxicity of existing treatment.

Treatment of unresectable, locally advanced NSCLC

Bimodality treatment : Chemotherapy and radiotherapy

Local treatment with radiotherapy (RT) alone gave disappointing results with 5 year survival rates less than 5% due to both locoregional and distant relapse. A meta-analysis of 1780 patients from 11 trials demonstrated that the addition of cisplatin-based chemotherapy (CT) to RT provided a small survival advantage of 4% at 2 years, and 2% at 5 years. The results of phase III studies of CT with RT compared to RT alone published after the NSCLC meta-analysis generally support that addition of CT to RT improves outcome.

CT can be given sequentially or concurrently with RT. Interest in the latter initially stemmed from the radiosensitising properties of cisplatin. For example The European Organisation for Research and Treatment of Cancer (EORTC) three-arm trial randomly assigned 331 patients to RT alone to 55 Gy, RT with weekly cisplatin (30 mg/m^2) or RT with daily cisplatin (6 mg/m^2) and achieved 2-year survival rates of 13% *v* 19% *v* 26% respectively (P = .04). However, the addition of low dose daily cisplatin improved local control with little impact on systemic relapse. The SWOG-9019 study was a phase II trial that evaluated full doses of cisplatin and etoposide concurrent with once-daily thoracic RT (45 Gy) in patients with pathological stage III NSCLC. In the absence of progressive disease, RT was completed to 61 Gy, with two additional cycles of cisplatin plus etoposide. The one, two, three and five year survivals achieved were 58%, 34%, 17% and 13% respectively with an overall median survival of 15 months (10-22 months).

Concurrent versus sequential chemoradiotherapy

The results of these studies overall indicate that concurrent CTRT is superior to sequential CTRT. Studies using concurrent CTRT report median survival times of 16 to 17 months as opposed to 13 to 14 months with sequential CTRT. However, this survival benefit is tempered by the increased toxicity encountered with concurrent treatment. For example in a study that evaluated cisplatin and etoposide concurrent

with RT then consolidation CT with cisplatin and vinorelbine compared to sequential cisplatin and vinorelbine followed by thoracic irradiation, the rate of grade 3/4 esophagitis was 26.1% *v* 0% and dysphagia 19.3% *v* 1% for the concurrent versus sequential arms.

Rationale for the CONCEPT trial : A Phase II Trial of pemetrexed consolidation after CTRT with cisplatin/etoposide

There is currently not an accepted standard chemoradiotherapy regimen for treatment of unresectable stage III NSCLC. Although the most promising regimen to date is the SWOG 9504 regimen this has not yet been proven in a phase III setting. In the SWOG 9504 trial 88% of the patients completed the concurrent CTRT phase, 78% proceeded to consolidation docetaxel, 75% of those starting consolidation received all three planned cycles and of these 41% achieved intended dose (initially 75 mg/m2 escalating to 100 mg/m2). Notably 57% of patients receiving consolidation chemotherapy developed grade 4 neutropenia, febrile neutropenia occurred in 9%, pneumonitis in 7% and three patients died of late pulmonary complications. Detailed quality of life analyses have not been reported for stage III concurrent CTRT trials however from the toxicity observed in the SWOG 9504 study it is intuitive that strategies to reduce the toxicity of treatment but maintain efficacy would be advantageous and may improve on the SWOG 9504.

Pemetrexed

Pemetrexed (pemetrexed disodium) (L-glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolol[2,3-d] pyrimidin-5-yl)ethyl] benzoyl]-, disodium salt) is a structurally novel, multitargeted, antifolate chemotherapy agent that is active in multiple tumour types including NSCLC. Its primary mechanism of action is to inhibit the enzyme thymidylate synthase, resulting in decreased thymidine necessary for pyrimidine synthesis. Pemetrexed also inhibits dihydrofolate reductase and glycinamide ribonucleotide formyl transferase, the latter of which is a folate-dependent enzyme involved in purine synthesis. Phase II studies of pemetrexed in previously untreated patients with NSCLC have demonstrated single agent response rates of 17 to 23 %, comparable with the single agent activity of docetaxel. In a phase III trial of pemetrexed versus docetaxel in 571 patients who had previously been treated with chemotherapy there was no significant difference in response rates (9.1% versus 8.8% respectively), median progression free survival (2.9 months both arms) or median survival time (8.3 versus 7.9 months respectively). The 1 year survival rate for each arm was 29.7%. In this trial there was a significant difference in the toxicity profiles for these drugs. Patients receiving docetaxel were more likely to encounter grade 3 or 4 neutropenia (40.2% versus 5.3%, $p < 0.001$), febrile neutropenia (12.7% versus 1.9%, $p < 0.001$), neutropenia with infections (3.3% versus 0.0%, $p = 0.004$), hospitalizations for neutropenic fever (13.4% versus 1.5%, $p < 0.001$), hospitalizations due to other drug related adverse events (10.5% versus 6.4%, $p = 0.092$), use of granulocyte colony-stimulating factor support (19.2% versus 2.6%, $p < 0.001$), and all grade alopecia (37.7% versus 6.4%, $p < 0.001$) compared with patients receiving pemetrexed.

The rationale for this trial is that pemetrexed is a less toxic, but equally active, alternative to docetaxel that can be administered following CTRT with cisplatin and etoposide. A less toxic consolidation CT may enable a higher proportion of patients to achieve planned dose which may improve outcome. Although a number of phase I and II trials are in progress to evaluate concurrent CTRT regimens with pemetrexed and platinum, the hypothesis that addition of pemetrexed following platinum and etoposide concurrent with RT has not been tested. The result of this trial will inform whether this regimen should be compared in future studies to the SWOG 9504 regimen if it proves superior to SWOG 9019 in the ongoing Hoosier Oncology Group trial and/or to a promising concurrent regimen employing pemetrexed.

3. Participants

Inclusion criteria

a) Histologically or cytologically confirmed NSCLC (mixed small cell, non-small cell histology is not permitted)
b) Inoperable Stage III disease (T4N0/1; T4N2; any TN3) confirmed by PET scanning, mediastinoscopy or thoracoscopy.
c) Tumour judged inoperable by a thoracic surgeon
d) Measurable or evaluable disease on CT scan
e) Age ≥ 18, no upper age limit
f) Performance status - ECOG 0 or 1 (appendix 1)
g) No prior chemotherapy, radiotherapy or investigational agents
h) Willing and able to give informed consent
i) Patient considered able to tolerate platinum based chemotherapy and radical radiotherapy:
   - Creatinine clearance ≥ 50 ml/min. The Cockcroft and Gault formula (see appendix 5) may be used to estimate GFR, but if <60 ml/min then EDTA clearance should be performed.
   - Adequate bone marrow reserve (i.e. white cell count > 4 x 10^9/l, absolute neutrophil count > 1.5 x 10^9/l, haemoglobin > 10.0 g/dl and platelet count >100 x 10^9/l).
   - Tumour that can be encompassed within a radical radiotherapy treatment volume (V_{20} expected to be < 35% - see section 4.3.2)
   - FEV1 ≥ 1.0 L or DLCO (transfer factor) ≥ 50% of predicted

Exclusion criteria

a) Stage IIIb wet (cytologically proven malignant pleural effusion). Pleural effusion permitted if it developed after exploratory surgery or

mediastinoscopy or if present only on CT scan and deemed too small to tap under ultrasound or CT guidance.

b) Pericardial effusion
c) Other previous or current malignant disease likely to interfere with protocol treatment or comparisons
d) Abnormal LFTs with any of: alkaline phosphatase, γGT, transaminases or bilirubin >1.5 times upper limit of normal range
e) Calcium above normal limits
f) Superior vena cava syndrome, haemoptysis causing a decrease in Hb of ≥1g/L
g) V20 > 35% (see section 4.3.2)
h) Medically unstable (e.g. unstable diabetes, uncontrolled arterial hypertension, infection, hypercalcaemia or ischaemic heart disease)
i) Patients who are pregnant or lactating.
j) Patients (of reproductive potential) who are unable to comply with effective contraception if sexually active during the study and for a period of at least 6 months after treatment.
k) Inability to interrupt aspirin or other nonsteroidal anti-inflammatory agents, other than an aspirin dose ≤ 1.3 grams per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam)."

4. Intervention

Treatment regimens

Etoposide
50 mg/m^2 BSA daily administered as an intravenous infusion over 10 minutes on day 1-5 and 29-33

Cisplatin
50 mg/m^2 BSA administered as an intravenous infusion over 60 minutes on day 1, 8, 29, 36

Consolidation pemetrexed
500 mg/m^2 BSA administered as slow iv bolus over 10 minutes on the first day of each 21 day cycle for 3 cycles on days 71, 92 and 113. (commencing a minimum of 3 weeks after radiotherapy is complete and not more than 6 weeks after completion of RT)

Radiotherapy

Dose specification and fractionation

Radical radiotherapy started on day 1 of the first cycle of chemotherapy.
The PTV received 60 Gy in 30 daily fractions of 2 Gy over a period of 40 days.

Premedication regimen

Folic Acid
Folic Acid (350-1000 µg) must be given daily beginning approximately 5-7 days prior to first doses of Alimta and continuing daily until 3 weeks after the last dose of study therapy.

Vitamin B12
Vitamin B_{12} (1000 µg) will be administered as an intramuscular injection approximately 1 to 2 weeks prior to first dose of Alimta and repeated approximately every 9 weeks until 3 weeks after the last dose of study therapy. After the first injection vitamin B_{12} injections may be given on the same day as pemetrexed

Dexamethasone
Dexamethasone (4 mg of oral or equivalent) given twice daily should be taken on the day before, the day of, and the day after each dose of pemetrexed (ALIMTA), for rash prophylaxis unless medically contraindicated.

Nonsteroidal Anti-Inflammatory Drugs
Patients taking NSAIDs will not take the NSAID 2 days before, the day of, and 2 days after pemetrexed administration. If a patient is taking an NSAID with a long half-life (for example, naproxen, piroxicam, diflunisal, or nabumetone), the NSAID should not be taken 5 days before, the day of, or 2 days after receiving pemetrexed. Concurrent use of aspirin is allowed, up to a maximum dose of 1.3 g per day.

5. Objectives

This was a phase II study to determine the 1-year survival of inoperable stage III patients with NSCLC given concurrent chemoradiotherapy (thoracic radiotherapy - 66 Gy in 6.5 weeks concurrently with 2 cycles of cisplatin/etoposide) followed by 3 cycles of consolidation pemetrexed.

Primary objective

- 1 year overall survival

Secondary objectives

- Progression free survival

- 2 year survival
- Late and acute Toxicity (CTCAE version 3.0-appendix 2)
- Compliance to treatment
- Response rate to concurrent CTRT

6. Outcomes

Objective response was measured according to the response evaluation criteria in solid tumours (RECIST).

Radiological assessment was made after every 2 cycles of chemotherapy.

All patients receiving $\geq$ 2 cycles of therapy and at least one follow-up assessment was considered evaluable for response unless progression occurred. Patients progressing earlier were evaluable as "early progression".

7. Sample size

Sample size was calculated using Fleming's single stage procedure, a one-sided test with alpha = 5% and the power at 80%. Taking the survival at 1-year to be at least 55% (below which no further investigation would be carried out), and the survival proportion that would warrant further investigation at 75%, would require 35 patients. Sequential patients presenting at the clinic who met the inclusion criteria were considered for the study and, after consent, enrolled by the clinic staff.

8. Methods

Summary tables are provided for patient demographics, baseline disease characteristics, compliance and toxicity. Overall survival was estimated according to the method of Kaplan and Meier. Continuous data was summarised using median, mean, minimum and maximum values. 95% confidence intervals calculated on proportions were provided by the exact method.
All patients had at least one dose of chemotherapy and were included in the survival analysis on an intention-to-treat basis. All patients received at least day 1 of concurrent chemotherapy and radiotherapy and were assessed for toxicity.
Overall Survival is the time between day 1 of cycle 1 and date of death of any cause. Survivors were censored on the last date known to be alive. Survival rates at 1-yr and 2-yr were compared with those of SWOG 9019 and SWOG 9504.

Local progression-free survival (local control) was calculated from day 1 of cycle 1 to the date of first clinical or radiological evidence of progressive disease at the primary site.
Progression-free survival (local or distant) was calculated from day 1 of cycle 1 to the date of first clinical or radiological evidence of progressive disease at any site.

Toxicity was assessed according to NCI Common Terminology Criteria for Adverse Events v 3.0 in all patients who were enrolled.

RESULTS

9. Participant flow

Treatment compliance

All 35 patients received at least day 1 of cycle 2 with concurrent chemo-radiotherapy (PE/RT), only one patient, who committed suicide, did not complete PE/RT, three patients had a dose reduction, two due to toxicity and one other medical condition and two were delayed, one for toxicity and one for admin reasons. No patients were given carboplatin in place of cisplatin. Full radiotherapy dose was delivered in 32/35 (91%) of patients, reasons (12,15,25 suicide). Three patients RT duration was in excess of 45 days, 46 (easter bank holiday), 47 (new year BH) and 52 (christmas and new year BH). Patients were given a minimum of three weeks and up to six weeks to recover from PE/RT before being considered for maintenance pemetrexed (PEM), 25/34 (74%) received at least day 1 cycle 1 of PEM. The reasons the nine patients not receiving PEM were, six for toxicity from PE/RT including a combination of oesophagitis, neutropenia, fatigue and mucositis, two patients' choice and one investigator's decision having a recurrent respiratory tract infection. Three patients did not receive cycle 2 PEM due to toxicity and six did not receive cycle 3, five because of toxicity and one patient died during cycle 2, 16/35(46%) of all patients completed all cycles, 16/25 (64%) of those commencing PEM, figure 1 and table 2.

10. Recruitment

Between March 2008 and October 2010, a total of 35 patients were entered into this study, all patients have had a least 12 months follow up.

Eligibility - two patients did not meet the criteria, one had a creatinine clearance of 43 (<50), investigator was aware and decided to proceed. The second had an FEV1 of 0.87 (<1.0)

11. Patient demographics

Table 1 presents patient demographics, the median age for all study participants was 61, ranging from 42 to 76. There were 23(66%) and 12(34%) males and females respectively. Sixty percent of patients had a histology of squamous cell carcinoma with

23% adenocarcinoma, 1 patient was stage IIB, 19/35(54%) of patients presented with stage IIIA disease and 43% had stage IIIB. ECOG performance status was 0 for 11/35(31%) and 1 for the remaining 69%. MRC respiratory score ranged from 0 to 3, 74% of patients were 0 or 1.

12. Numbers analysed

All 35 patients were included for survival. For toxicity to PE/RT all 35 were included, the 25 who received at least day 1 of maintenance pemetrexed were assessed for PEM toxicity.

13. Safety analysis

Non-haematological toxicity

Table 3 shows non-haematological toxicity overall and during each phase of PE/RT and PEM. The number of patients experiencing grade 3 non-haematological toxicities was small in the PE/RT phase, 4/35(11%) and 2/35(6%) of patients reported nausea and vomiting, respectively. Grade 3 mucositis was experienced by 3/35(9%) as was anorexia, 8/35(23%) had grade 3 infection and 6/35(17%) had grade 3 fatigue. The only grade 3 in the PEM phase was 5(20%) with infection and two patients with fatigue, there were no grade 4 non-haematological toxicities. Both phases were well tolerated.

Acute and Late radiation toxicity

Acute radiation toxicity during the PE/RT phase is shown in table 4, 23/34(68%) had grade 2 and 10/34(29%) of patients experienced grade 3 oesophagitis. There was one grade 4 acute pneumonitis. (Updated Jan2014)

At 6 months post PE/RT 2(7%) of patients had grade 3 late oesophageal strictures and one patient each had grade 3 and 4 late pneumonitis and one patient had pulmonary fibrosis. Other grade 3/4 toxicities included cavitating lesion, lung cavity infection, pulmonary embolism, hearing loss, chest pain and anorexia. At 12m post PE/RT one patient had grade 2 late oespophagitis, 17(68%) had grade 1,2 pneumonitis and one had grade 3. Other radiation induced toxicities include the two patients continuing with oesophageal strictures from 6 month assessment. As late toxicity is difficult to

distinguish from symptoms and disease progression these figures were revised see new table 4 below (Jan2014)

Haematological toxicity, Transfusions, Antibiotics and Hospitalisation

Haematological toxicity is summarized in table 5. In both phases a high proportion of patients had at least grade 1/2 anaemia with 1/35(3%) during PE/RT and 3/25(12%) during PEM having grade 3/4. More patients had grade 3/4 leucopenia and neutropenia during the PE/RT phase, 54% and 49%, while during the PEM phase only 16% and 8% experienced grade 3/4. Forty-six percent of patients had grade 1/2 thrombocytopenia with 1/35(3%) during PE/RT having grade 4.

During the PE/RT phase two patients required blood transfusions and 7(28%) during PEM phase, no patients required platelet transfusions. IV antibiotics were required by 9/35(26%) of patients during PE/RT and 5/25(20%) during PEM. Two patients received GCSF support during PE/RT. Additional overnight stays in hospital were required for 15/35(43%), 191 nights and 8/25(32%), 93 nights for each phase respectively, table 6. These additional hospitalization days were reported as serious adverse events such as atrial fibrillation, cellulitis of left arm, two patients with grade 3 oesophagitis, raised temperature, uncontrolled pain and dehydration, febrile neutropenia and tachycardia, suspected myocardial infarction during PE/RT and pulmonary fibrosis and pneumonitis (died), rash, grade 3 oesophagitis, grade 3 neutropenic sepsis, chest infection during PEM, all expected in this disease population.

There were no unexpected serious adverse events reported.

Survival

As of 1 July 2012, 18 patients were still alive and median follow-up for these patients was 753 days (25 months). Estimated median survival for deaths from all causes (including suicide pt) was 1021 days (34 months), 1-year 77% (95% ci 60%, 88%), 2-year 61% (95%ci 37%, 72%) table 8 and figure 4. (See revised figures below Jun2013)

To date 21/35 (60%) patients have relapsed either locally or distant or both with a median PFS of 661 days (22 months), 1-yr 62% (95% c.i. 43%, 76%).
The number of patients documented as relapsing locally only was 16/35(46%) with a median local progression free survival of 870 days (29 months), 1-yr 73% (95% c.i. 53%, 86%), table 8. (See revised figures below Jun2013)
There were two toxic deaths, one from pneumonitis and one from a massive haemoptysis.

Post study treatment

To date four patients have received palliative radiotherapy, two patients received tarceva, others were referred for palliative care. Reasons for ending study are given in table 9.

15. Data collection summary

Completion of worksheets during the study was inconsistent, with data having to be found amongst annotations and collected retrospectively, subsequently case report forms completed by data managers well after the patients had come off study or died had some missing and inconsistent data. The relatively small numbers in the study made it possible to relocate the patient notes which would not have been possible in a larger study.
One of the reasons for this was the duration of the study, over time personnel changed and they were unfamiliar with the appropriate forms to complete. Consequently, there were no early checks on source data collection or clarification of any misinterpretation of variables to be collected or to resolve any problems that occurred with collecting good quality data.
It is important to emphasize that Investigator-led studies have to follow the same guidelines as commercially sponsored studies and it is important to locate and complete the relevant forms in a timely manner.

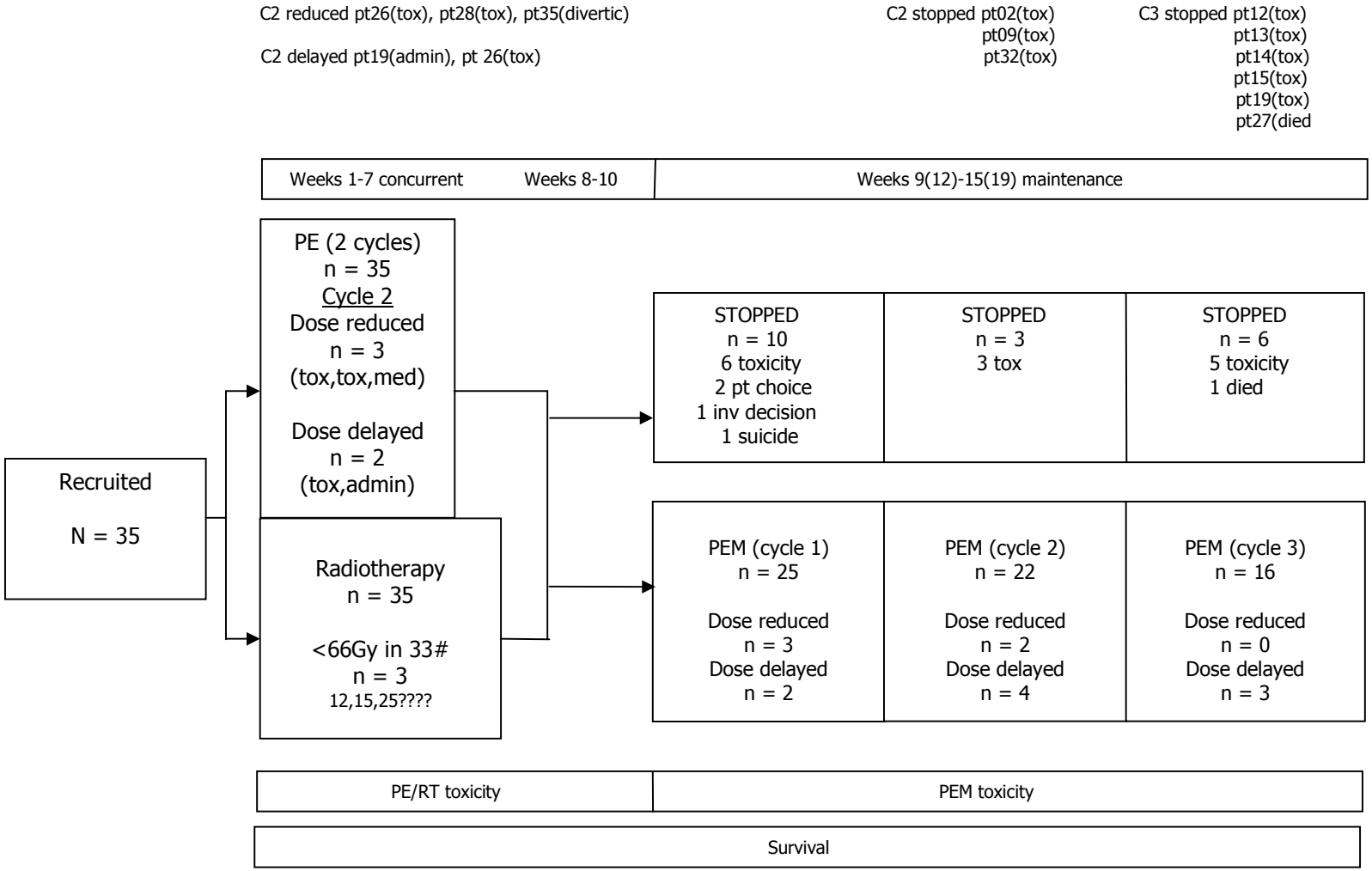
16. Comparison of CONCEPT with SWOG9019 and 9504

Median, 1-yr and 2-yr survival for CONCEPT are comparable with those of SWOG 9504 and better than those for 9019, table 10. Neutropenia grade 3/4 was 48% for this study compared to 58% and 74%, oesophagitis was slightly higher 29% but the maximum grade was 3 and there one death from pneumonitis, none from infection, table 11.

The completion rate of concurrent CTRT for SWOG 9504 was 88%, in this study there was a 97% completion rate for concurrent PE/RT. Those continuing on to the maintenance phase were 78% and 71% respectively for SWOG 9504 and CONCEPT with 75% and 64% receiving all 3 intended cycles and of those 41% and 64% received intended dose, table 12.

It would appear from the results of our study that they are comparable with SWOG 9405 and superior to SWOG 9019 and the regimen would be an ideal candidate to use in the design of a future study in stage III NSCLC.

Figure 1



12 Hashmet Ali
15 Rosemary Storrie planned with AMRT 1 day late starting /50% heart 50% dose?

red 1 gr3 hiccups (75%)
1 pt choice (gson) (80%)
del 2 tox, 1 pt ch

del 2 tox

25	Suicide	1 admin	1 med (Teflon)

Table 1 Patient demographics for all patients

Arm		**All**
n		**35 (%)**
Age	**Median** **Range**	61 (42,76)
Gender	**Male** **Female**	23 (66) 12 (34)
Histology	**Squamous** **Adeno** **Undiff** **Other**	21 (60) 8 (23) 4 (11) 2 (6)
Stage	**IIB** **IIIA** **IIIB**	1 (3) 19 (54) 15 (43)
ECOG PS	**0** **1**	11 (31) 24 (69)
MRC RS	**0** **1** **2** **3** ***n/a***	14 (40) 12 (34) 7 (20) 1 (3) *1 (3)*

Table 2 Treatment compliance for all patients

Chemotherapy	**Cycles**	
n		**35 (%)**
PE	1	1 (3)*
	2	34 (97)
Concurrent RT	66Gy in 33# 63Gy in 33# 59Gy in 30# 56Gy in 28#	32 (91) 1 (3)~ 1 (3)# 1 (3)*
Pemetrexed	0	10 (29)
	1	25 (71)
	2	22 (63)
	3	16 (46)

*Pt death (suicide) ~Pt15 #Pt12

Table 3 Non-haematological toxicity by study phase

Max Toxicity	grade	PE/RT	PEM	All TREAT
n		**35**	**25**	**35**
nausea	**0**	10 (29)	12 (48)	8 (23)
	1,2	21 (60)	13 (52)	23 (66)
	3,4	4 (11)	-	4 (11)
vomiting	**0**	19 (54)	22 (88)	17 (49)
	1,2	14 (40)	3 (12)	16 (45)
	3,4	2 (6)	-	2 (6)
constipation	**0**	19 (54)	21 (84)	19 (54)
	1,2	16 (46)	4 (16)	16 (46)
	3,4	-	-	-
diarrhoea	**0**	33 (94)	21 (84)	30 (86)
	1,2	2 (6)	4 (16)	5 (14)
	3,4	-	-	-
alopecia	**0**	4 (11)	8 (32)	4 (11)
	1,2	31 (89)	17 (68)	31 (89)
	3,4	-	-	-
mucositis	**0**	10 (29)	17 (68)	10 (29)
	1,2	22 (62)	8 (32)	22 (62)
	3,4	3 (9)	-	3 (9)
anorexia	**0**	11 (31)	13 (52)	6 (17)
	1,2	21 (60)	12 (48)	26 (74)
	3,4	3 (9)	-	3 (9)
infection	**0**	21 (60)	12 (48)	14 (40)
	1,2	6 (17)	8 (32)	12 (34)
	3,4	8 (23)	5 (20)	9 (26)
sensory	**0**	24 (69)	18 (72)	21 (60)
	1,2	11 (31)	7 (28)	14 (40)
	3,4	-	-	-
rash	**0**	34 (97)	20 (80)	29 (83)
	1,2	1 (3)	5 (20)	6 (17)
	3,4	-	-	-
fatigue	**0**	1 (3)	1 (4)	1 (3)
	1,2	28 (80)	22 (88)	26 (74)
	3,4	6 (17)	2 (8)	8 (23)
hearing loss	**0**	24 (69)	21 (84)	22 (63)
	1,2	11 (31)	4 (16)	13 (37)
	3,4	-	-	-
renal	**0**	31 (91)	22 (96)	31 (89)
	1,2	3 (9)	1 (4)	3 (9)
	3,4	-	-	-
	n/k			1 (2)

Table 4 Acute/Late radiation toxicity (See end for revised tables Jun 2013/Jan2014)

Max toxicity	**grade**	**Acute**	**Late (6m)**	**Late (12m)**
n		**35**	**29**	**27**
oesophagitis	**0**	1 (3)	27 (93)	25 (96)
	2	23 (68)	2 (7)	1 (4)
	3,4	10 (29)	-	-
	n/a	1	-	1
pneumonitis	**0**	29 (85)	2 (7)	7 (28)
	1,2	5 (15)	23 (82)	17 (68)
	3,4	-	2 (7)	1 (4)
	5	1	1 (4)	-
	n/a		1	2
pulmonary	**0**	32 (94)	-	-
infiltrates/	**1,2**	2 (6)	26 (96)	23 (100)
fibrosis	**3,4**	-	1 (4)	-
	n/a	1	2	4
spinal cord	**0**		29 (100)	25 (100)
	1,2		-	-
	3,4		-	-
	n/a			2
<u>Other grade 3,4</u>				
cavitating lesion		-	1	1
lung cavity infect		-	1	1
PE		-	1	-
hearing loss		-	1	-
chest pain		-	1	-
anorexia		-	1	-
oesoph stricture		-	2	2

Table 5 Haematological toxicity by study phase

Max toxicity	grade	PE/RT	PEM	ALL TREAT
n		**35**	**25**	**35**
Hb	**0**	2 (6)	-	1 (3)
	1,2	32 (91)	22 (88)	30 (86)
	3,4	1 (3)	3 (12)	4 (11)
WCC	**0**	2 (6)	11 (44)	2 (6)
	1,2	14 (40)	10 (40)	13 (37)
	3,4	19 (54)	4 (16)	20 (57)
neutrophils	**0**	4 (11)	14 (56)	4 (11)
	1,2	14 (40)	9 (36)	14 (40)
	3,4	17 (49)	2 (8)	17 (49)
platelets	**0**	18 (51)	22 (88)	18 (51)
	1,2	16 (46)	3 (12)	16 (46)
	3,4	1 (3)	-	1 (3)

Hb		gr3 gr4	2 1	
WCC		gr3 gr4	4 -	
neutrophils		gr3 gr4	1 1	

Table 6 Transfusions/Antibiotics/Hospitalisation(Extra overnight stays)

Pts requiring:		PE/RT	PEM
n		**35**	**25**
blood transfusions	**no**	33 (94)	18 (72)
	yes	2 (6)	7 (28)
Total units required		4	21
platelets transfusions	**no**	35 (100)	25 (100)
	yes	-	-

Pts requiring:		PE/RT	PEM
n		**35**	**25**
IV +/- oral abx	**no**	26 (74)	20 (80)
	yes	9 (26)	5 (20)
oral abx only	**no**	26 (74)	15 (60)
	yes	9 (26)	10 (40)

Pts requiring:		PE/RT	PEM
n		**35**	**25**
GCSF	**no**	33 (94)	25 (100)
	yes	2 (6)	-

Pts requiring:		PE/RT	PEM
n		**35**	**25**
hospitalisation	**no**	20 (57)	17 (68)
	yes	15 (43)	8 (32)
Total extra nights		191	93

During PE Hospitalisation	atrial fibrillation, cellulitis left arm, 2 x gr 3 oesph, raised temp, uncon pain and dehydration, feb neutropenia and tachycardia, suspected myocardial infarction
During PEM Hospitalisation	pulmonary fib and pneumoitis (died), rash, gr 3 oesophagitis, gr 3 neutropenic sepsis, chest infection

Table 8 Overall survival from all causes/local progression free survival (see below revised Jun2013)

Overall	**Overall survival**
n	**35**
Median (days)	1021 (34 mths)
1-year (95% ci)	77% (60%,88%)
2-year (95% ci)	61% (37%,72%)
Local	**Local progression free survival**
No of pts documented local relapse	16 (46%)
Median (days)	870 (29 months)
1-year (95% ci)	73% (53%,86%)
2-year (95% ci)	57% (36%,73%)
Any progression (local and/or distant)	**Progression free survival**
No of pts documented with progression	21 (60%)
Median (days)	661 (22 months)
1-year (95% ci)	62% (43%,76%)
2-year (95% ci)	49% (31%,65%)

Table 9 Reasons for ending study

	completed PE + conRT	**PEM**			
		none	**completed only 1 cycle**	**completed only 2 cyles**	**completed all 3 cycles**
n	**34**	**9**	**3**	**6**	**16**
patient choice		2			
inv decision		1			
toxicity		6	3	5	
progressed/died	1*			1#	

*unrelated medical condition #treatment related haemoptysis

Table 10. Survival comparison of all three studies

Survival	**CONCEPT**	**SWOG 9019**	**SWOG 9504**
	35	**50**	**83**
median	34 mths	15 mths	26 mths
1-yr	77%	58%	76%
2-yr	58%	34%	54%
3-yr	(32%)	17%	37%

Table 11. Acute toxicity comparison of all three studies

Toxicity	**CONCEPT**		**SWOG 9019**		**SWOG 9504**	
N	**35**		**50**		**83**	
grade	**3**	**4**	**3**	**4**	**3**	**4**
Neutropenia	11 (31%)	6 (17%)	13 (26%)	16 (32%)	17 (20%)	45 (54%)
Thrombocytopenia	0	1 (3%)	3 (6%)	3 (6%)	6 (7%)	0
Oesophagitis	10 (29%)	0	6 (12%)	4 (8%)	10 (12%)	4 (5%)
Pneumonitis	0	0	0	0	4 (5%)	2 gr5
Infection	9 (26%)	0		2 gr5		2 gr5

Table 12. Compliance comparison

	CONCEPT	**SWOG9504**
Completing concurrent CT/RT	97%	88%
Pemetrexed/docetaxel	71%	78%
All 3 cycles	64%	75%
Intended dose	64%	41%

Figure 2

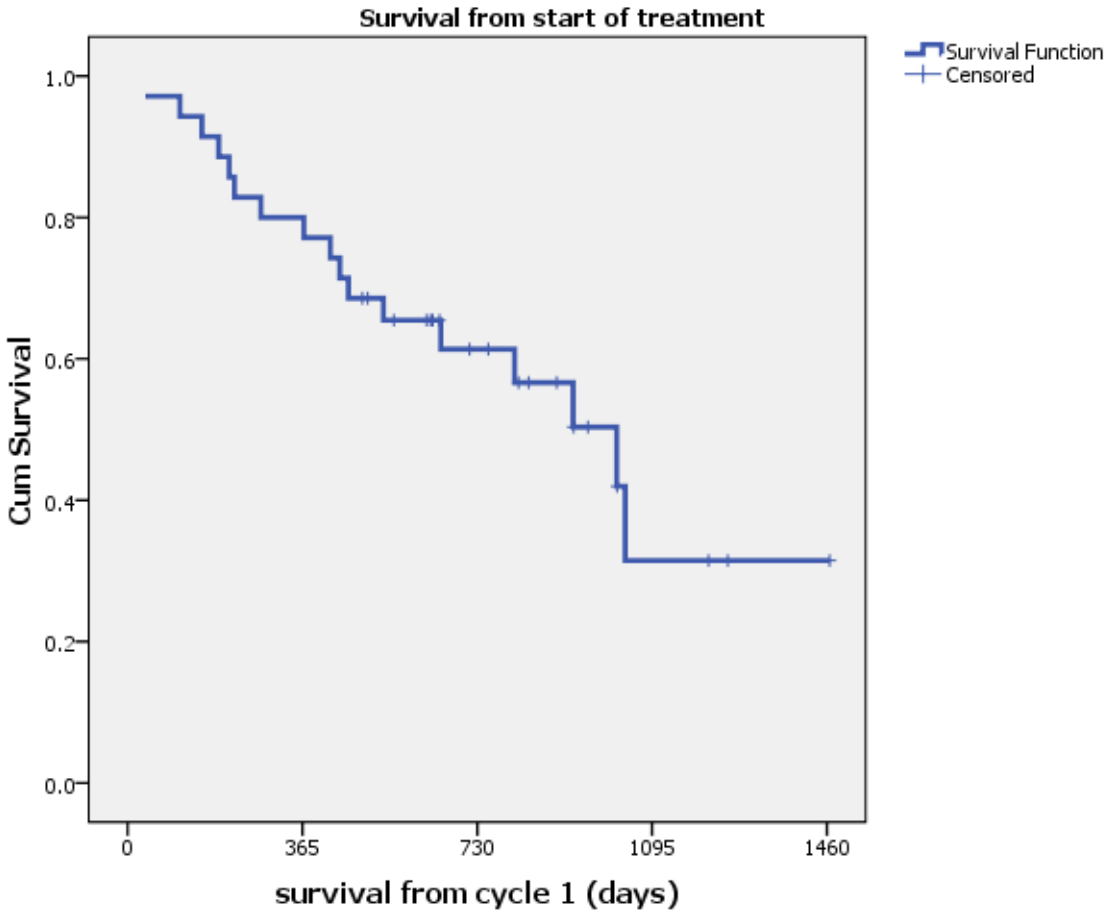
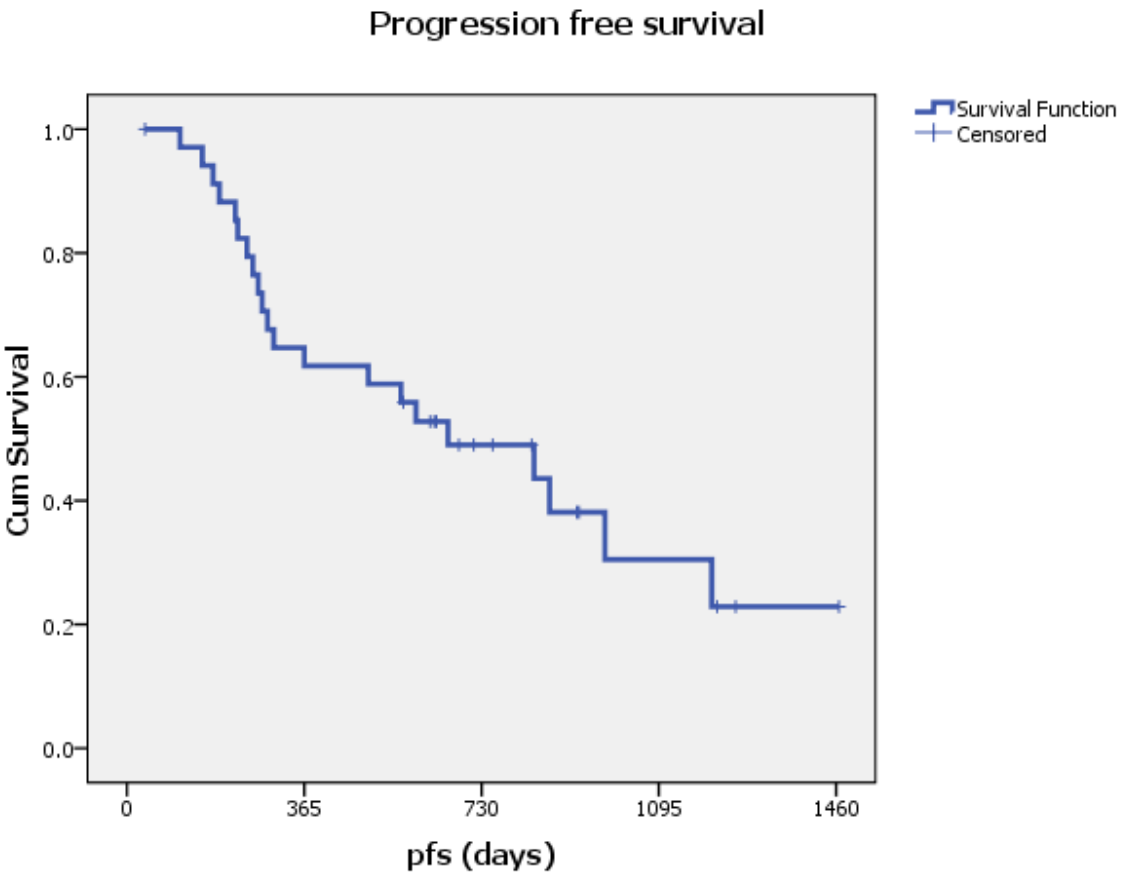

Survival from start of treatment
Survival Function
Censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
365
730
1095
1460
survival from cycle 1 (days)

Figure 3.


Progression free survival
Survival Function
Censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
365
730
1095
1460
pfs (days)

For information only

Radiotherapy parameters

	Median	Min	Max
Total dose Gy	66.0	56.0	68.0
Min PTV dose Gy	52.7	28.5	60.7 (0.96)
No of fractions	33	28	33
No of beams	4	3	8
Energy (Mv)	6		
PTV cms3	464.4	284.1	946.8
GTV cms3	60.2	11.4	274.4
V5% lung	59.6	19.1	78.9
V20% lung	30.4	10.5	35.3 (≤35)
Mean Lung Dose Gy	18.3	8.5	25.9
Spinal cord max dose Gy	43.8	25.5	73.5 (≤48)
Max dose to oesophagus	66.3	51.7	71.9
Length of oesophagus	8.4	0.0	18.6 (≤12)

Four patients had a duration of RT delivery >45days, 46, 46, 47 and 52 days, all were due to bank holidays, the first two, one day holidays, the third two days over new year and the latter seven days over Christmas and new year.

Table 4 Acute/Late radiation toxicity (See end for revised tables Jun 2013)

Max toxicity	grade	Acute	Late (6m)	Late (12m)
n		**35**	**29**	**27**
oesophagitis	**0**	1 (3)	25 (87)	25 (96)
	2	23 (68)	2 (7)	1 (4)
	3	10 (29)	1 (3)	-
	4	-	1 (3)	-
	n/a	1	-	1
Pneumonitis*	**0**	29 (85)	2 (7)	7 (28)
	1,2	5 (15)	23 (87)	17 (68)
	3	-	1 (3)	1 (4)
	4	1	1 (3)	-
	n/a		2	2
pulmonary infiltrates/ fibrosis	**0**	32 (94)	-	-
	1,2	2 (6)	26 (96)	23 (100)
	3	-	1 (4)	-
	4	-	-	-
	n/a	1	2	4
spinal cord	**0**		29 (100)	25 (100)
	1,2		-	-
	3		-	-
	4		-	-
	n/a			2
Other grade 3,4				
cavitating lesion		-	1	1
lung cavity infect		-	1	1
PE		-	1 (gr4)	-
hearing loss		-	1	-
chest pain		-	1	-
anorexia		-	1	-
oesoph stricture		-	-	2

*Late pneumonitis is difficult to distinguish between symptoms and disease progression therefore only acute toxicity will be displayed in table format, other late toxicities will be described in text format in the final report, see below. (CFF 9/1/14)

Table 4 Acute radiation toxicity (See end for revised tables Jan2014)

Max toxicity	**grade**	**Acute**
n		**35**
oesophagitis	**0**	1 (3)
	2	23 (68)
	3	10 (29)
	4	-
	n/a	1
Pneumonitis	**0**	29 (85)
	1,2	5 (15)
	3	-
	4	1
	n/a	
pulmonary infiltrates/ fibrosis	**0**	32 (94)
	1,2	2 (6)
	3	-
	4	-
	n/a	1

Table 8 Overall survival from all causes/local progression free survival (see below revised Jun2013)

Overall	**Overall survival**
n	**35**
Median (days)	1021 (34 mths)
1-year (95% ci)	77% (60%,88%)
2-year (95% ci)	61% (37%,72%)
Local	**Local progression free survival**
No of pts documented local relapse	16 (46%)
Median (days)	870 (29 months)
1-year (95% ci)	73% (53%,86%)
2-year (95% ci)	57% (36%,73%)
Distant	**Distant progression free survival**
No of pts documented distant relapse	17 (49%)
Median (days)	1021 (34 months)
1-year (95% ci)	74% (54%,86%)
2-year (95% ci)	62% (36%,73%)
Any progression (local and/or distant)	**Progression free survival**
No of pts documented with progression	21 (60%)
Median (days)	661 (22 months)
1-year (95% ci)	62% (43%,76%)
2-year (95% ci)	49% (31%,65%)

Table * Status at July 2012 (see below revised Jun2013)

Status	**N**	**Cause of death**
Alive	**19**	n/a
Intercurrent death	**1**	suicide
Toxic death	**2**	pneumonitis massive haemoptysis
Lung ca death	**13**	Lung ca

Updated survival data 26/06/2013

Survival

As of 26 June 2013, 9 patients were still alive and median follow-up for these patients was 1015 days (33 months). Estimated median survival for deaths from all causes (including suicide pt) was 930 days (31 months) (95% ci 19m, 42m), 1-year 77% (95% ci 60%, 88%), 2-year 57% (95%ci 39%, 72%), 3-yr 36% (95%ci 20%, 53%).

To date 25/35 (71%) patients have relapsed either locally or distant or both with a median PFS of 629 days (21 months) (95% ci 9m, 33m), 1-yr 62% (95%ci 43%, 76%), 2-yr 44% (95% c.i. 27%, 60%).

The number of patients documented as relapsing locally only was 18/35(51%) with a median local progression free survival of 952 days (31 months), 1-yr 73% (95% c.i. 53%, 86%), 2-yr 59% (95% c.i. 39%, 74%).

Table * Status at June 2013 (revised Jun2013)

Status	**N**	**Cause of death**
Alive	**9**	n/a
Intercurrent death	**1**	suicide
Toxic death	**2**	pneumonitis massive haemoptysis
Lung ca death	**23**	Lung ca

Added 20-Jan-2014

Sorry Linda-another query on CONCEPT from fiona

thanks

corinne

The median follow-up was 25 months. As of 26 June 2013, nine patients were still alive and median follow-up for these patients was 33 months.

FHB's comment
Confusing – need to give median follow up for all – and that in June 2013 X had died with a median fu of and X alive with median FU

In June 2013 the median follow up for all patients was 44 mths (95% c.i. 36,51). There were 9 patients still alive at this date with a median FU of 33 months ranging from (28, 54) months.

Update 10-Feb-2014 (Mar-2014)

The survival and progression medians etc have not changed since previous analysis June 2013, the only exception is that there are now eight patients still alive rather than 9 up to 66 months. Eighteen patients were documented as progressing locally and 9 distantly. Twelve had further treatment, three were treated with Erlotinib(Tarceva) either on or off study, three with docetaxel and three with gemcitabine/carboplatin, of these two also had radiotherapy and two had radiotherapy alone, one patient had a pneumonectomy and another had an oesophageal stent inserted and later had talc pleurodesis.

From: Finn Corinne (RBV) NHS Christie
Sent: 10 February 2014 14:28
To: Ashcroft Linda (RBV) NHS Christie Tr
Subject: RE: CONCEPT update

Thanks
Do we have data whether local progression was in field/ out of field ?
Do we know if the patients referred for surgery actually had surgery? if you do not have the data I can look into it

corinne

The site of local progression is coded as:
(1=NO 2=YES)

WITHIN HIGH	WITHIN LOW	OUTSIDE AND WITHIN	OUTSIDE AND OUTSIDE	NO OF PTS (18)
1	1	2	1	1
1	1	1	2	1
2	1	1	1	7
2	1	1	2	2
2	2	1	1	2
2	2	2	1	2
9	9	9	9	3

Medway states the patient had a right pneumonectomy at Wythenshawe in Dec 2012 he is recorded as progressing locally Jul2012..

Mar 2014

Status	**N**	**Cause of death**
Alive	**8**	n/a
Intercurrent death	**1**	suicide
Toxic death	**3**	pneumonitis massive haemoptysis radiotherapy effects
Lung ca death	**23**	Lung ca