THE RISK AND COSTS OF FEBRILE NEUTROPENIA IN PATIENTS WITH NON SMALL CELL LUNG CANCER TREATED WITH DOCETAXEL

REPORT BY THE NICE DECISION SUPPORT UNIT.

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SUMMARY

Following a Single Technology Appraisal (STA) of erlotinib (Tarceva®, Roche) for non small cell lung cancer and subsequent appeal, NICE commissioned the Decision Support Unit (DSU) to consider evidence on several parameters in relation to docetaxel, the comparator to erlotinib in this appraisal. This report presents the results of a systematic review and meta analysis of the probability of febrile neutropenia associated with docetaxel. Estimates of the cost of treating febrile neutropenia are provided and these revised estimates incorporated into the Roche cost effectiveness model by the Evidence Review Group (LRiG).

Thirteen studies were identified and a random effects meta analysis conducted. The pooled, random effect meta-analysis estimate for the proportion of patients who experience one or more episodes of FN on docetaxel is 5.95% (95% CI 4.22 to 8.31). The costs of treating febrile neutropenia are based on hospitalisation and intravenous antibiotics for the majority of patients, while a small proportion receive oral antibiotics combined with a short period of hospitalisation. The cost of treating each episode of febrile neutropenia was estimated as £2,286. No evidence of significant use of granulocyte colony-stimulating factors (G-CSFs) in the UK NHS was identified either for treatment or prophylaxis.

Using these parameter values generates a cost per additional Quality Adjusted Life Year (QALY) of £48,038.

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1. BACKGROUND

Erlotinib (Tarceva® - Roche) for the treatment of non small cell lung cancer (NSCLC) has recently been appraised by the Institute under the Single Technology Appraisal (STA) process. The Appraisal Committee concluded at their meeting of 11th January 2007 that erlotinib should not be recommended for use in the NHS for the treatment of NSCLC. An appeal was held on the 6th July 2007, where it was concluded that the Institute should undertake extra analyses in relation to the comparator, docetaxel.

Docetaxel is considered to be associated with a risk of febrile neutropenia (FN) which can be both costly to treat and have substantial quality of life implications. Consequently, the risk of febrile neutropenia in the comparator drug docetaxel may be an important driver in the assessment of cost-effectiveness for erlotinib (Taxotere® - Sanofi-Aventis).

This report addresses three questions in relation to FN and docetaxel as specified by the appeal panel. Firstly, what is the risk of FN associated with docetaxel in NSCLC? Secondly, what is the typical cost of treating FN in the UK NHS? Thirdly, what is the impact on the estimates of cost effectiveness of erlotinib when these new estimates are included in the manufacturer model?

2. FEBRILE NEUTROPENIA ASSOCIATED WITH DOCETAXEL

2.1. THE PROBABILITY OF FEBRILE NEUTROPENIA

In the original manufacturer submission, the probability that a patient treated with docetaxel experiences at least one episode of FN was 1.8% based on a single study (Hannah et al. 2004). At the appeal hearing (NICE, Appeal hearing Decision of the Panel) Dr Mike Cullen, representing The Royal College of Physicians and the Association of Cancer Physicians "believed from a study of his own, published in the New England Journal of Medicine, that the true rate of febrile neutropenia with docetaxel was 18%." (para 135).

In this section, we review the evidence of the incidence of FN in patients receiving docetaxel as second line therapy for NSCLC.

2.1.1. Search strategy for review of FN rates

A comprehensive search was undertaken to identify literature on docetaxel use in lung cancer. Searches were not restricted by language, publication date or publication type. Databases searched were Medline, Medline in Process, EMBASE and The Cochrane Library including the Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register (CENTRAL), DARE, NHS EED and HTA databases. The search strategy for EMBASE was modified to included additional terms around "Neutropenia" as omitting these terms resulted in an unmanageable result set of limited specificity. The search strategies are included in Appendix 1.

2.1.2. Inclusion criteria

Studies were included if they assessed the use of docetaxel as monotherapy, in patients with NSCLC who had received one or more previous chemotherapy regimens for their disease. These criteria were chosen so as to reflect as far as possible the NSCLC patient group for which docetaxel treatment is recommended in the UK.

Systematic reviews were included so that a manual search could be conducted of their reference lists in order to ensure all relevant studies had been identified. Studies that met the inclusion criteria above but were only published as abstracts or as conference presentations were not included in the review unless a full paper could be obtained that related to the abstract.

2.1.3. Data extraction

The main variable of interest from the clinical effectiveness studies is the rate of febrile neutropenia among patients in the docetaxel arms of the studies, in particular among those patients receiving the standard recommended dose (75mg/m^2 as a one-hour infusion every three weeks). In addition, it is important to know if patients received granulocyte colony-stimulating factors (G-CSFs), following chemotherapy as this would be expected to reduce the incidence of FN events. No information was available in relation to the use of prophylactic antibiotics, although since many of the

identified studies were conducted prior to the publication of one of the major trial of prophylactic antibiotics (Cullen et al. 2005) this is unlikely to be a significant issue. Additional information regarding the baseline characteristics of the study samples and description of survival outcomes and treatment duration provides a more complete picture which can be helpful when there is substantial variation in rates between studies. Full data extraction tables will therefore be included in the results section, as well as summary tables of FN rates.

2.1.4. Results

In total, 8 phase III RCTs were identified and 5 phase II studies (Table 1). No data from non randomized sources were identified. Five studies compared the clinical effectiveness of standard docetaxel (75mg/m²) with a weekly infusion of docetaxel at a lower dose: Gridelli 2004; Schuette 2005; Camps 2006; Gervais 2005; and Chen 2006. Two studies compared combination irinotecan + docetaxel with standard dose docetaxel: Wachters 2005 and Pectasides 2005. One study assessed standard dose docetaxel compared with topotecan: Ramlau 2006. One study compared two doses of docetaxel (75mg/m² and 100mg/m²) with vinorelbine or ifosfamide: Fossella 2000. One study investigated standard dose docetaxel with pemetrexed: Hanna 2004. One study compared two doses of docetaxel (75mg/m² and 100mg/m²) with best supportive care: Shepherd 2000. One study assessed two doses of docetaxel: Quoix 2004 and one study compared oral gefitinib with standard dose docetaxel: Cufer 2006.

Two systematic reviews which considered the use of docetaxel in NSCLC were identified: Clegg et al. (2001) and Horn et al. (2007). Literature searches had been conducted in 2000 and 2005 for Clegg and Horn, respectively. Both reviews were used as a check that all studies for those periods had been identified in the updated literature search.

In the manufacturers most recent submission (Roche, 31st October 2007) two studies were included which did not meet the inclusion criteria for this review. One is a study abstract by Ramlau (2007) for which a full study paper is not available (FN probability =5%). The second is a study by Douillard et al. (2007) whose results were presented at the World Conference on Lung Cancer, September 2007 but which has

not yet been published (FN probability =10.1%). The details of febrile neutropenia in this study do not appear in the abstract.

Table 1: Identified studies of clinical effectiveness of second line monotherapy docetaxel in NSCLC

Study (n)	Intervention
Phase III studies	
Gridelli 2004 N=220	Docetaxel 75mg/m^2 one infusion every 3 weeks for six cycles vs. docetaxel 33.3mg/m^2 weekly for 6 weeks and 2 weeks rest for two cycles. Further therapy discretional.
Schuette 2005 N=215	Docetaxel 75mg/m^2 one infusion every 3 weeks vs. docetaxel 35mg/m^2 weekly for 3 weeks and 1 week rest. Patients to receive a maximum of 8 cycles of their regime.
Camps 2006 N=259	Docetaxel 75mg/m^2 one infusion every 3 weeks vs. docetaxel 36mg/m^2 one infusion every week for 6 weeks followed by 2 week rest. Treatment continued until disease progression or unacceptable toxicity.
Ramlau 2006 N=829	Oral topotecan 2.3 mg/m^2/d on days 1 to 5 (Top) vs. IV docetaxel 75 mg/m^2/d one infusion every 3 weeks for at least four cycles. Additional cycles permitted.
Fossella 2000 N=373	Docetaxel 100mg/m^2 one infusion every 3 weeks vs. docetaxel 75mg/m^2 one infusion every three weeks vs. vinorelbine once weekly for 3 weeks or ifosfamide on days 1 to 3 of every 3-week cycle. Treatment continued after 6 cycles if condition satisfactory.
Hanna 2004 N=571	Pemetrexed 500mg/m^2 as an infusion vs. docetaxel 75mg/m2 one infusion every 3 weeks. Treatment continued until disease progression or unacceptable toxicity.
Shepherd 2000 N=103*	Docetaxel 100mg/m^2 one infusion every 3 weeks vs. docetaxel 75mg/m2 one infusion every 3 weeks vs best supportive care (BSC). Treatment continued until disease progression or unacceptable toxicity.
Chen 2006 n=161	Docetaxel 35 mg/m^2 IV infusion on days 1, 8, and 15 every 4 weeks vs. docetaxel, 40 mg/m^2 IV on days 1 and 8 every 3 weeks vs. docetaxel, 75 mg/m^2 every 3 weeks. Treatment continued until disease progression or unacceptable toxicity.
Phase II studies	
Cufer 2006 n=141	Gefitinib oral dose of 250 mg/day vs. IV docetaxel 75 mg/m^2/d on day 1 every 3 weeks. Treatment continued until disease progression or unacceptable toxicity.
Pectasides 2005 n=130	Docetaxel 75mg/m^2 one infusion every 3 weeks vs. docetaxel 30 mg/m^2 (1-h infusion) and irinotecan 60 mg/m^2 (90-min infusion) on days 1 and 8, both administered every 3 weeks. Treatment continued until disease progression or unacceptable toxicity.
Quoix 2004 n=183	Docetaxel 100mg/m^2 one infusion every 3 weeks vs. docetaxel 75mg/m2 one infusion every 3 weeks Study planned for 6 cycles and further treatment could be given at physician's discretion.
Gervais 2005 n=125	Docetaxel 75mg/m^2 one infusion every 3 weeks vs. docetaxel 40mg/m^2 weekly for 6 weeks and a two week rest. Treatment continued until disease progression or unacceptable toxicity.
Wachters 2005 n=108	Docetaxel 75mg/m^2 one infusion every 3 weeks vs. docetaxel 60mg/m^2 plus irinotecan 200mg/m^2 as one infusion every 3 weeks. Treatment given for a maximum of 5 cycles.

* The initial dose of 100mg/m^2 was reduced to 75mg/m^2 because of a high toxic death rate at the higher dose level.

Table 2 below presents further details of each study including: description of study populations; treatment duration; median survival; and use of prophylactic G-CSFs.

Table 2: Full data extraction tables for studies meeting inclusion criteria

Study	Study sample*	Interventions	Number of cycles administered	Survival	Rate of febrile neutropenia % of patients	Use of prophylactic G-CSFs
Camps 2006 Spain RCT phase III	Median age=61.5 Stage IIIB=16.1% Stage IV=83.9% ECOG % 0=18 1=66, 2=16. >1 prior chemo=15%	Docetaxel 75mg/m^2 one infusion every 3 weeks (D75) n=131 vs. docetaxel 36mg/m^2 one infusion every week for 6 weeks followed by 2 week rest (D36) n=128. Treatment continued until disease progression or unacceptable toxicity.	Median no. of cycles in D75 group=3 and D36=1	Median survival in months: D75=6.6 vs.. D36=5.4	D75=7.8% and D36=0.8%	This study does not report the use or non-use of G-CSFs.
Fossella 2000 USA RCT phase III	Median age=59₸ Stage IIIA/B=NR Stage IV=90%₸ ECOG % 2=18 (others NR).₸ ≥2 prior chemos=26%₸	Docetaxel 100mg/m^2 one infusion every 3 weeks (D100) n=125 vs. docetaxel 75mg/m^2 one infusion every three weeks (D75) n=125 vs. vinorelbine on days 1,8 and 15 of every 3-week cycle or ifosfamide on days 1 to 3 of every 3-week cycle (V/I) n=123. Treatment continued after 6 cycles if condition satisfactory.	Median no. of cycles administered in D100 and D75 groups=3 and in V/I groups =3/2.	Median survival in months: D100=6.6, D75=5.8, and V/I=5.4	D100=12%, D75=8% and V/I=1%	Filgrastim either prophylactic or therapeutic was used in 28% of cycles in D100 group, 7% of cycles in the D75 group and 3% of cycles in the V/I group.
Gridelli 2004 Italy RCT phase III	Median age=63 Stage IIIB=14% Stage IV=86% ECOG % 0=32 1=52, 2=16. >1 prior chemo=0%	Docetaxel 75mg/m^2 one infusion every 3 weeks for six cycles (D75) n=110 vs. docetaxel 33.3mg/m^2 on days 1,8,15,22,29 and 36 every 8 weeks (6 weeks of treatment followed by 2 weeks of rest) for two cycles (D33.3) n=110. Further therapy was discretional.	69% of D75 patients received at least 3 cycles and 23% 6 cycles. 62% of D33.3 received 1 cycle (6 administrations) and 25% received 2 cycles.	Median survival in weeks: D75=29 and D33.3=25.	D75=5% and D33.3=0%	Prophylactic use of haemopoietic colony stimulating factors was not allowed.
Hanna 2004 USA RCT phase III	Median age=57₸ Stage IIIA/B=NR Stage IV=75% ECOG % 0 or 1=87.6 , 2=12.4. ₸ >1 prior chemo=0%	Pemetrexed 500mg/m^2 as an infusion (Pem) n=283 vs. docetaxel 75mg/m2 as an infusion (Doc) n=288 on day 1 of a 21-day cycle. Treatment continued until disease progression or unacceptable toxicity.	Median no. of cycles in each group =4	Median survival in months: Pem=8.3 and Doc=7.9	Pem=1.9% and Doc=12.7%	G-CSF used as prophylaxis in 4 Doc patients vs. 1 Pem patient. In the Doc and Pem groups n=49 and n=5 were treated with G-CSF for neutropenia, respectively.
Ramlau 2006 International RCT phase III	Mean age=59 Stage IIIb=NR Stage IV=73% ECOG % 0=17 1=68, 2=15, 3=0, 4=<1. >1 prior chemo=<1%	Oral topotecan 2.3 mg/m^2/d on days 1 to 5 (Top) n=414 vs. IV docetaxel 75 mg/m^2/d on day 1 every 3 weeks (Doc) n=415, for at least four cycles. Additional cycles permitted.	Median no. of cycles in Top group = 3 and Doc=4	Median survival in weeks: Top=28 vs. Doc=31	Top=4% and Doc=3%	G-CSFs were administered to 22 (6%) patients in the Top group and 30 (8%) patients in the Doc group.
Schuette 2005	Median age=63 Stage IIIA/B=NR	Docetaxel 75mg/m^2 one infusion every 3 weeks (D75) n=103 vs. docetaxel 35mg/m^2 on days 1, 8, and 15 of a	Median no. of cycles in D75 group=4 and D35=2	Median survival in months: D75=6.3 and	D75=2.0% and D35=1.0%	G-CSF used at the physician's discretion. Numbers who used G-CSF

Germany RCT phase III	Stage IV=NR ECOG % 0=33 1=53, 2=11. Others NR. >1 prior chemo=100%	28-day cycle (D35) n=105. Patients to receive a maximum of 8 cycles of their regime.		D35=9.2		not reported.
Shepherd 2000 Canada RCT phase III	Median age=61 Stage IIIA/B=21.1% Stage IV=78.9% ECOG % 0=19 1=56, 2=25. >1 prior chemo=25%	Docetaxel 100mg/m^2 one infusion every 3 weeks (D100) n=49 vs. docetaxel 75mg/m2 one infusion every 3 weeks (D75) n=55 vs. best supportive care (BSC) n=100.** Treatment continued until disease progression or unacceptable toxicity.	Median no. of cycles in D100 group= 2, D75=4	Median survival in months: Docetaxel=7.0 vs. BSC=4.6	D100=22.4% ** and D75=1.8%	This study does not report the use or non-use of G-CSFs.
Chen 2006 Taipei RCT phase III	Median age=64 Stage IIIB=9.1% Stage IV=91% ECOG % 0=0 1=39, 2=61. >1 prior chemo=9.1%	Docetaxel 35 mg/m2 IV infusion (D35) on days 1, 8, and 15 every 4 weeks (D35) n=64 vs. docetaxel, 40 mg/m2 IV on days 1 and 8 every 3 weeks (D40) n=64 vs. docetaxel, 75 mg/m2 every 3 weeks (D75) n=33. Treatment continued until disease progression or unacceptable toxicity.	Median no. of cycles in D35 group=4 , D40 group=3 and D75=4	Median survival in months: D35=8.4 vs. D40=7.2 vs. D75=9.5	D35=1.6% and D40=4.7 D75=12.1	Study reports that patients with febrile neutropenia (n=1,3, and 4 in each study arm) were treated with G-CSF but does not otherwise report the use of G-CSFs.
Cufer 2006 International RCT phase II	Median age=59.5 Stage III=NR Stage IV=56% ECOG % 0=16 1=50, 2=33. >1 prior chemo=0%	Gefitinib oral dose of 250 mg/day (Gef) n=68 vs. IV docetaxel 75 mg/m^2/d on day 1 every 3 weeks (Doc) n=73. Treatment continued until disease progression or unacceptable toxicity.	Median no. of cycles not reported.	Median survival in months: Gef=7.5 vs. Doc=7.1	Gef=0% and Doc=3.2%	This study does not report the use or non-use of G-CSFs.
Pectasides 2005 Greece RCT phase II	Median age=59 Stage IIIA/B=NR Stage IV=NR ECOG % 0=30 1=56, 2=14. >1 prior chemo=0%	Docetaxel 75mg/m^2 one infusion every 3 weeks (D75) n=65 vs. docetaxel 30 mg/m^2 (1-h infusion) and irinotecan 60 mg/m^2 (90-min infusion) on days 1 and 8, both administered every 3 weeks (Comb) n=65. Treatment continued until disease progression or unacceptable toxicity.	Median no. of cycles in D75 group= 3 and Comb group=3	Median survival in months: D75=6.5 and Comb=6.4	D75=5% and Comb=5%	Therapeutic or prophylactic G-CSF was used by 18 patients (28%) in the D75l arm and 22 patients (34%) in the Comb arm.
Quoix 2004 France RCT phase II	Median age=59 Stage IIIA/B=26% Stage IV=57% ECOG % 0=16 1=60, 2=24. >1 prior chemo=NR	Docetaxel 100mg/m^2 one infusion every 3 weeks (D100) n=89 vs. docetaxel 75mg/m2 one infusion every 3 weeks (D75) n=94. Study planned for 6 cycles and further treatment could be given at physician's discretion.	Median no. of cycles in D100 group= 3 and D75 group=2	Median survival in months: D100=6.7 vs. D75=4.7	D100= 6.8% and D75=6.7%	This study does not report the use or non-use of G-CSFs.
Gervais 2005 France	Median age=59 Stage IIIA/B=34% Stage IV=66%	Docetaxel 75mg/m^2 one infusion every 3 weeks (D75) n=62 vs. docetaxel 40mg/m^2 weekly for 6 weeks and a two week rest (D40) n=63. Treatment continued until	Median no. of cycles in D75 group=3 and D40 group=1	Median survival in months: D75=5.8 vs. D40=5.5	D75=6.5% and D40=0%	G-CSFs not authorized at cycle 1

RCT phase II	ECOG % 0=14 1=66, 2=21. >1 prior chemo=0%	disease progression or unacceptable toxicity.				
Wachters 2005 Netherlands RCT phase II	Median age=59 Stage IIIA/B=23% Stage IV=77% ECOG % 0=21 1=70, 2=8.3. >1 prior chemo=NR	Docetaxel 75mg/m^2 one infusion every 3 weeks (D75) n=56 vs. docetaxel 60mg/m^2 plus irinotecan 200mg/m^2 as one infusion every 3 weeks (Comb) n=52. Treatment given for a maximum of 5 cycles.	Median no. of cycles in D75 group=4 and Comb group= 3	Median survival in weeks: D75=32 vs. Comb=27	D75=5% and Comb = 6%	Lenograstim was administered in all patients on days 2 to 12.

G-CSF=granulocyte-colony stimulating factors, ECOG=Eastern Cooperative Oncology Group performance status: 0=asymptomatic, 1=symptomatic but completely ambulant, 2=symptomatic <50% in bed during the day, 3= Symptomatic, >50% in bed, but not bed bound, 4=bed bound, 5=death. NR=Not reported

* For brevity data reported for study sample as a whole when available. Otherwise data for docetaxel group was used (T)

** The initial dose of 100mg/m^2 one infusion every 3 weeks was reduced to 75mg/m2 one infusion every 3 weeks because of a high toxic death rate at the higher dose level.

NR=Not reported

Table 3 shows rates of febrile neutropenia by docetaxel dose in studies which did not use G-CSFs for prophylaxis. Table 4 presents rates of FN in the same way for studies in which patients were prescribed G-CSFs. It should be noted that in the study by Shepherd et al 2000 (Table 3) when interim safety-data monitoring identified a significantly higher toxic death rate in the chemotherapy arm of the study, the protocol was amended and the docetaxel dose was reduced from 100mg/m^2 to 75 mg/m^2 given intravenously over 1 hour every 3 weeks for the second half of the trial. Excluding the FN rate for docetaxel dose 100mg/m^2 in the Shepherd 2000 study, FN rates ranged from 0% to 7.8% in studies that did not use G-CSFs.

Table 3: Rates of febrile neutropenia in docetaxel studies for NSCLC in which no G-CSF used

Study	Docetaxel dose (n in study arm)	Treatment duration	% of patients with an FN event
Gridelli 2004 N=220	1) One infusion 75mg/m^2 every 3 weeks. 2) One infusion 33.3mg/m^2 every week for 6 weeks and 2 weeks rest.	69% received 3 cycles (9 wks) and 23% 6 cycles (18 wks) 62% received 1 cycle (8 wks) and 25% received 2 cycles (16 wks)	5 (NR/110) 0 (NR/110)
Shepherd 2000 N=103	1) One infusion 100mg/m^2 every 3 weeks. 2) One infusion 75mg/m^2 every 3 weeks.	Median no. of cycles=2 (6 weeks) Median no. of cycles=4 (12 weeks)	22.4* (11/49) 1.8 (1/55)
Camps 2006 N=259	1) One infusion 75mg/m^2 every 3 weeks. 2) One infusion 36mg/m^2 every week for 6 weeks and 2 weeks rest.	Median no. of cycles=3 (9 weeks) Median no. of cycles=1 (8 weeks).	7.8 (10/129) 0.8 (1/125)
Cufer 2006 N=141	One infusion 75mg/m^2 every 3 weeks.	Median no. of cycles not reported	3.2 (2/63)
Quoix 2004 N=183	1) One infusion 100mg/m^2 every 3 weeks. 2) One infusion 75mg/m^2 every 3 weeks.	Median no. of cycles = 3 Median no. of cycles = 2	6.8 (6/88) 6.7 (6/89)
Gervais 2005 N=125	1) One infusion 75mg/m^2 every 3 weeks. 2) One infusion 40mg/m^2 every week for 6 weeks and 2 weeks rest.	Median no. of cycles = 3 Median no. of cycles = 1	6.5 (4/62) 0 (0/63)

** The initial dose of 100mg/m^2 one infusion every 3 weeks was reduced to 75mg/m^2 one infusion every 3 weeks because of a high toxic death rate at the higher dose level.*

In studies that included the use of G-CSFs, rates of FN ranged from 1% to 12.7% (Table 4)

Table 4: Rates of febrile neutropenia in docetaxel studies for NSCLC in which G-CSF used

Study	Docetaxel dose (number in study arm)	Treatment duration	Rates of FN (% of patients)
Fossella 2000 N=373	1) One infusion 100mg/m^2 every 3 weeks. 2) One infusion 75mg/m^2 every 3 weeks.	Median no. of cycles=3 Median no. of cycles=3	12 (NR/121) 8 (NR/121)
Hanna 2004 N=571	One infusion 75mg/m^2 every 3 weeks.	Median no. of cycles=4	12.7 (NR/126)
Schuette 2005 N=215	1) One infusion 75mg/m^2 every 3 weeks. 2) One infusion 35mg/m^2 every week for 3 weeks and 1 weeks rest.	Median no. of cycles=4 Median no. of cycles=2	2.0 (2/102) 1.0 (1/105)
Ramlau 2006 N=829	One infusion 75mg/m^2 every 3 weeks.	Median no. of cycles=4	3 (11/401)
Chen 2006 N=161	1) One infusion 35mg/m^2 every week for 3 weeks and 1 weeks rest. 2) One infusion 40mg/m^2 every week for 3 weeks and 1 weeks rest. 3) One infusion 75mg/m^2 every 3 weeks.	Median no. of cycles=4 Median no. of cycles= 3 Median no. of cycles= 4	1.6 (1/64) 4.7 (3/64) 12.1 (4/33)
Pectasides 2005 N=130	One infusion 75mg/m^2 every 3 weeks.	Median no. of cycles=3	5 (3/65)
Wachters 2005 N=108	One infusion 75mg/m^2 every 3 weeks.	Median no. of cycles=4	5 (3/56)

In all trials FN events are presented as the percentage of patients experiencing FN. The trials do not report the number of events per person. In most studies when a patient had an adverse event such as an FN event, chemotherapy treatment was either delayed or the dose was modified. Therefore it is reasonable to assume that some patients will have gone on to have another FN event during treatment. But unfortunately, we have no way of knowing this from the data reported in the trials. Nor do we know during which chemotherapy cycle the FN event (or events) occurred.

Table 5 summarises FN rates for standard doses of docetaxel: that is, 75 mg/m2 given intravenously over 1 hour every 3 weeks. In studies which did not prescribe G-CSFs, FN rates for patients treated with the recommended standard dose of docetaxel ranged from 1.8% to 7.8%. In studies which prescribed G-CSFs, FN rates ranged from 2.0% to 12.7%.

Table 5: Febrile neutropenia rates with recommended regime of docetaxel: 75mg/m2 given intravenously once every 3 weeks

Study	% of patients with FN	G-CSF use in standard dose arm
No G-CSFs used:		
Shepherd 2000	1.8 (1/55)	
Gridelli 2004	5 (NR/110)	
Camps 2006	7.8 (10/129)	
Cufer 2006	3.2 (2/63)	
Quoix 2004	6.7 (6/89)	
Gervais 2005	6.5 (4/62)	
G-CSFs used:		
Fossella 2000	8 (NR/121)	Prophylactic or therapeutic used in 7% of cycles
Hanna 2004	12.7 (NR/126)	Prophylactic use in 4(1.4%) patients and as treatment in 49(17%)
Schuette 2005	2.0 (2/102)	Used at physician's discretion. No data on actual use reported.
Ramlau 2006	3 (11/401)	Administered to 30 (8%) of patients
Chen 2006	12.1 (4/33)	Used as treatment for all patients with FN, n=4 (12.1%)
Pectasides 2005	5 (3/65)	Therapeutic or prophylactic used by 18 (28%) of patients
Wachters 2005	5 (3/56)	Lenograstim administered to all patients on days 2 to 12

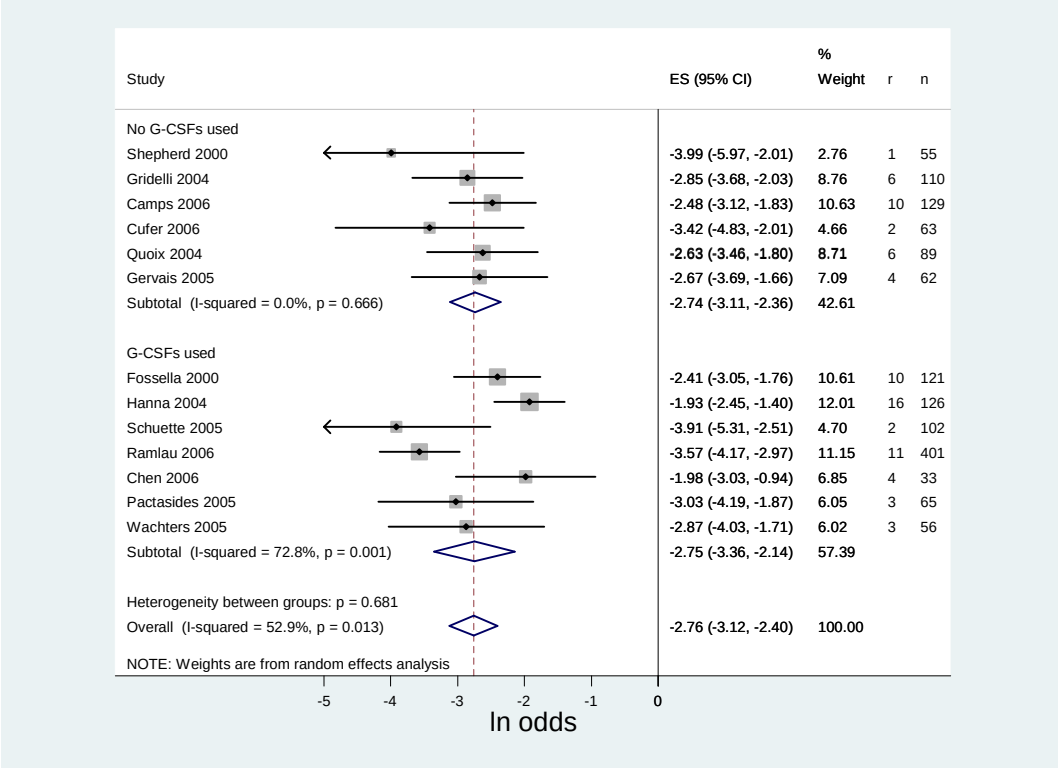
Meta analysis

Meta-analysis was conducted on the 13 study arms described in Table 5. Some numerator data for the percentage of patients with FN were not reported but these were derived directly using the denominators and percentages reported in the papers. Only one figure was equivocal – the numerator for Gridelli – since 5 or 6 events would provide a percentage rounding up or down to 5%. 6 events were imputed in this instance. Hence the data used in the meta-analysis is provided in Figure 1.

Due to between study heterogeneity, a random effect meta-analysis was conducted. Analysis was conducted on the ln(odds) scale and transformed back to the proportion scale for interpretation. Given the varying use of G-CSF's among patients a subgroup analysis comparing studies with any G-CSF use with no use was conducted as well as an overall analysis (Figure 1). While percentages in both groups were almost identical, the majority of the observed heterogeneity was in the group which had some G-CSF use. The pooled, random effect meta-analysis estimate for the proportion of patients who experience one or more episodes of FN on docetaxel is 5.95% (95% CI 4.22 to 8.31).

A further subgroup analysis was carried out combining phase III and phase II trials separately. Pooled estimates were similar from both with the majority of the heterogeneity being observed in the phase 3 studies.

Figure 1: Forest plot for ln(odds) of experiencing FN on standard dose docetaxel (75mg/m2 given intravenously once every 3 weeks)



- Overview

All the evidence identified comes from randomized controlled trials. However, the analysis is based only on the intervention arms, not the comparators. No observational data was identified.

Several stakeholders also submitted evidence. No published evidence was suggested by stakeholders that was not identified in this review, with one exception. Dr Rodney Burnham on behalf of the Royal College of Physicians cites 9 phase 3 trials of docetaxel. All these studies are included with the exception of Ramlau (2005) and Ramlau (2007). No reference list is provided so we have been unable to check these citations. The quoted probability of FN in these studies is 3% and 5% respectively.

Conference abstracts have not been included in this review for the following reasons:

1) full data enabling inclusion in the meta-analysis was not available for some studies.
2) These studies were not identified through systematic methods and there is a risk that the inclusion of such studies may be particularly susceptible to pipeline biases, that is, the tendency for significant results to be published more quickly than less significant ones.
3) it is not clear that measures refer to the numbers of patients experiencing at least one episode of FN.

Douillard et al. (2007) is a conference abstract that does not itself contain data on FN. A PowerPoint presentation does contain data on FN and this is a relatively high rate (10.1%) compared to other studies. However, it should be noted that other conference abstracts were suggested by Roy Castle Lung Cancer Foundation and Cancerbackup and these have lower FN risks than Douillard et al. (2007). These are Kizakowski et al. (2007) which cites a 5% incidence of FN in the docetaxel arm of the trial (n=277), and Fidias et al. (2007) which cites a 2.8% incidence of FN in patients receiving docetaxel immediately after induction therapy (n= 153). Two other abstracts were suggested by these consultees. One was not considered relevant (Hannah 2007) and one had insufficient detail to allow us to identify the abstract.

The following unpublished evidence was submitted.

- Data from the Christie hospital shows that 12/82 (15%) patients receiving docetaxel received IV antibiotics. This data does not state that patients had a diagnosis of FN. It is not stated whether each of these episodes relate to different patients.
- Data from the Royal Marsden hospital reports a rate of 8.9% (7/79) over 6 years. The outcome measure is neutropenic sepsis/febrile neutropenia (not cancer symptoms related)
- Data from the Velindre hospital states that one patient from twelve (8%) required admission with FN. This was across 40 chemotherapy cycles.
- the appeal panel received evidence of a rate of 18% FN in a study by Dr Michael Cullen. These data do not appear in the NEJM paper this figure is attributed to (Cullen et al. 2005) and we have not been unable to verify this data with Dr Cullen. Dr Cullen has stated that there were less than 20 patients receiving docetaxel and with NSCLC in this study. It is not clear if

the figure of 18% quoted in the appeal panel documentation refers to this small patient subgroup or another group of patients.

2.2. THE MEAN NUMBER OF EPISODES OF FN

There is evidence that the risk of febrile neutropenia is highest at cycle 1 and then decreases over subsequent cycles in breast cancer (von Minckwitz et al. 2007) and in small cell lung cancer (Timmer-Bonte et al. 2005) but that for patients that have already had an FN event the relative risk of a further event is higher. The Roche model does not explicitly consider this issue but instead incorporates a mean 2.4 FN events for patients that experience FN at all. The figure of 2.4 is based on expert opinion.

Timmer Bonte et al. (2005) provide sufficient detail to calculate the mean number of episodes per patient. For patients in the control arm of this trial (who received prophylactic antibiotics), the mean number of FN episodes per patient with FN across all cycles is 1.44. For patients receiving G-CSFs in addition to antibiotics (the intervention arm), the ratio is similar – 1.31. The mean number of episodes was 1.4 for all patients combined. It should be noted that whilst these patients were all receiving prophylaxis of some type, which may differ from NHS practice for NSCLC, this prophylaxis was given across each chemotherapy cycle. Therefore, unless the relative effectiveness of prophylactic antibiotics, with or without G-CSFs, differs across cycles, then these figures will also provide an accurate estimate of the mean number of episodes per patient that develops FN but does not receive prophylaxis of any type across all cycles.

3. THE COST OF TREATING FEBRILE NEUTROPENIA

In the original submission by Roche, the treatment cost per episode of neutropenia was estimated as £3,582 based on a UK study (Holmes et al. 2004). In the revised Roche submission, FN costs are estimated as £4,781.

In order to calculate the typical cost of treating FN in the NHS in patients with NSCLC, we have addressed the following questions:

a) To what extent do patients receive granulocyte colony-stimulating factors (G-CSFs) either as treatment, primary or secondary prophylaxis?

b) What is the probability of hospitalisation with FN?
c) What is the mean length of stay for patients hospitalised?
d) What is the cost of IV antibiotics?

3.1. THE USE OF G-CSFS IN THE UK NHS

G-CSFs, which include Neulasta (pegfilgrastim), Neupogen (filgrastim) and lenograstim, have been shown to reduce the incidence of FN when used as prophylaxis and may also be used as a treatment for FN. Prophylaxis can take the form of primary prophylaxis, defined as G-CSF given for all chemotherapy cycles, beginning in the first cycle, or secondary prophylaxis, defined as G-CSF given in all chemotherapy cycles following an FN event. However, the administration and drug acquisition costs are high, and there is uncertainty about the extent to which G-CSFs are actually used in the UK NHS in the NSCLC population.

The European EORTC guidelines for G-CSFs (Aapro et al 2006), and the ASCO (Smith et al. 2006) and NCCN guidelines (2006), recommend that prophylactic G-CSFs should be used where the overall risk of FN is $\geq$ 20%, taking into account both the chemotherapy regimen and patient risk factors. Where the risk is 10-20%, individual patient characteristics should be considered which may increase the overall risk. Evidence presented above suggests that the risk across all cycles of docetaxel is unlikely to warrant the use of prophylactic G-CSFs according to these guidelines.

We were unable to identify any published evidence relating to the use of G-CSFs for patients with NSCLC using docetaxel. A UK audit of 422 breast cancer patients (Leonard et al, 2003) found that 5.2% of patients received G-CSF, either as treatment for FN (1.7%) or as secondary prophylaxis (3.6%). Given that there is a number of chemotherapy regimens widely used in breast cancer associated with FN risks in excess of 20%, it appears that G-CSFs may currently be underused in the UK in relation to European guidelines.

We spoke directly to five clinical experts (Wolverhampton, Liverpool, Nottingham and two from Sheffield) for their views about G-CSF use in this patient population in their own practices and more broadly across the NHS. All clearly stated that the use of

G-CSFs for this patient population (i.e. NSCLC taking docetaxel) would only be in exceptional circumstances. For example, where a patient had experienced two or three previous episodes of FN and prophylactic antibiotics at the previous cycle had failed to prevent a further episode. Clinicians did not consider docetaxel as "high-risk" in relation to FN and given the relatively high cost of G-CSFs, did not believe their routine use was appropriate in the NHS.

In addition, three NHS Trusts documents were identified through an internet search (Dartford and Gravesham NHS Trust, East and North Hertfordshire NHS Trust, Surrey, West Sussex and Hampshire Cancer Network). One document states "the use of prophylactic G-CSF for patients undergoing palliative chemotherapy should be avoided, and dose reduction should be considered to prevent further neutropenic episodes and sepsis" (East and North Hertfordshire). The other two documents recommend that G-CSFs only be used in situations where treatment is being given with curative intent. (Dartmouth and Gravesham NHS Trust as well as West Sussex, Surrey and Hampshire NHS Trust).

Therefore, our conclusion is that the use of G-CSFs as either treatment or prophylaxis of FN in this patient population is not typical in the NHS and therefore should not be included as a cost attributable to docetaxel. This is in direct contrast to the evidence submitted by Roche which suggests that both treatment and secondary prophylaxis with G-CSFs is widespread in the NHS based on interviews with 6 centres across England (p.12) although results are presented for 8 centres.

Other information submitted by consultees is mixed. Evidence submitted by Dr Nick Thatcher from the Christie hospital states that the treatment protocol for febrile neutropenia includes treatment with GCSF if patients neutrophil count has not increased after 2 days (the submission assumes that this would apply to 10% of patients). In addition, secondary prophylaxis with GCSF is then used for subsequent docetaxel cycles. It may be the case that this evidence is included in the Roche data since Dr Thatcher was a member of the expert panel meeting which estimated resource use for the original submission.

Evidence from Dr Fergus Macbeth from the Velindre Hospital states that GCSF treatment is only recommended for patients with toxic shock as treatment and other use is for secondary prophylaxis, although the criteria for use is not stated.

3.2. THE PROBABILITY OF HOSPITALISATION WITH FN

The NCCN guidelines on prevention & treatment of cancer-related infections (2007) recommend that all patients at high-risk for development of serious medical complications during the episode should be treated as inpatients with IV antibiotics, while low-risk patients may be treated with oral antibiotics, and possibly as outpatients. Risk scores which attempt to categorise patients according to low or high risk do exist (Klastersky et al. 2000), although the extent to which these are used in practice is variable in the UK NHS.

There is some evidence to suggest that not all patients with FN are hospitalised. A US study (Ozer et al 2007) of 971 breast cancer patients receiving a minimum of 4 chemotherapy cycles and receiving G-CSFs in all cycles found that the percentage of patients having FN was 3.2% in cycle 1 and 6.1% across all cycles. However, the percentage of patients with FN-related hospitalisation was 1.0% in cycle 1 and 3.2% across all cycles. This implies that only 52% of patients having FN at any time were hospitalised (and 31% of patients having FN in cycle 1).

An alternative approach for the treatment of low-risk FN patient is for oral antibiotics to commence in hospital but for patients to be discharged early. Innes et al. (2007) report their experience of using the MASCC risk index to classify FN patients as high or low risk. 90% of 100 episodes were classified as low risk and treated with oral antibiotics and early hospital discharge. The median duration of hospitalisation was reduced from 6.5 days (25^{th} centile 5.3 days; 75th centile: 9.3 days) to 2.5 days (25th centile: 1.0 day; 75^{th} centile: 5.0 days).

Klatersky et al. (2000) report a prospective multinational study of febrile neutropenic cancer patients (n= 1139) used to develop the MASCC risk index. Using the authors' chosen cut-off of a score of 21 for low-risk vs. high-risk, 551 of 756 patients in the derivation set (73%), and 243 of 383 patients in the validation set (63%) were

classified as low-risk. Overall across both groups in this study, 794 of 1139 patients (70%) were classified as low-risk.

Innes et al. (2005) report a survey of UK cancer clinicians to identify the extent to which risk stratification occurs in clinical practice and the extent to which oral antibiotics and early hospital discharge for these patients occurs. They found that 38% of clinicians (from n=128) perform some type of risk stratification of FN patients but only 22% use oral antibiotics. This study was performed in 2003, just 3 years after publication of the MASCC risk-index. It is likely that uptake of this treatment approach has increased over time and this estimate is therefore likely to be conservative.

We therefore assume that whilst 70% of patients with FN may be classified as low risk, the maximum proportion of these that will receive oral antibiotics and early hospital discharge is 0.154 (0.7 x 0.22).

3.3. DURATION AND COST OF HOSPITALISATION

3.3.1. HIGH RISK PATIENTS

Timmer-Bonte et al. (2006), in a study of small cell lung cancer set in the Netherlands (N=175) found that the mean length of FN hospitalisation was 8.5 days for patients not receiving G-CSFs (N=20) and 7 days for patients receiving G-CSFs (N=9) at the first cycle. These figures are derived from Table 1 of the paper which reports the mean length of hospitalization across all patients i.e. including those that were not hospitalized for FN.

Crawford et al. (1991) (cited in Lyman et al. 2004) report a mean length of stay of 10 days (n=206) for lung cancer patients. However, this is not restricted to patients with a primary diagnosis of FN. Lyman et al. (2004) present data that if FN is the not the first (primary) diagnosis then the associated length of stay is much higher.

Evidence from other cancer types suggests that the estimate by Timmer Bonte et al. (2006) is a fair estimate.

Kuderer et al. (2006) looked at FN hospitalisations in the US between 1995 and 2000 in 3077 breast cancer patients. The mean length of hospitalisation was 8 days (SD: 0.4).

Caggiano et al. (2005) evaluated chemotherapy-induced neutropenia hospitalizations (not restricted to FNs) from 1,000 hospital discharges for breast cancer from 1999 in the US. The mean length of hospitalisation was 5.6 days (SD 5.6).

Cullen et al. (2005), in the placebo arm of a trial of prophylactic antibacterials in the UK across a range of chemotherapies and cancers, report a median duration of hospitalization of 5 days (interquartile range 3-8 days) for those hospitalised with a febrile episode (n=130).

We therefore use the estimate from Timmer Bonte et al. (2006) for patients not treated with G-CSFs (8.5 days) and suggest that results also incorporate the cost of 5 days inpatient treatment based on Cullen et al. (2005).

The evidence presented by Timmer Bonte et al. (2006) has implications for the methods used by Roche to identify a unit cost of FN. Roche include widespread use of G-CSFs both as treatment and prophylaxis in terms of increased costs. Timmer Bonte et al. (2006) demonstrate that G-CSFs reduce the mean length of stay but because the Roche approach uses a tariff value, this reduction in resource use would not be reflected in the cost estimate. G-CSFs only increase the cost of treatment in the Roche model, there is no offset for reduced length of stay.

The mean length of stay in the audit data (n=10) submitted by Dr Nick Thatcher on behalf of the Roy Castle Lung Cancer Foundation is clearly influenced by three outliers whose length of stay exceeds 30 days. It is questionable that these hospitalisations are solely attributable to FN. In addition, the patient group is mixed in terms of treatment with G-CSFs which, as demonstrated by Timmer Bonte et al. (2006), would influence the length of stay. Excluding these outliers gives a mean length of stay of 7.1 days.

3.3.2. LOW RISK PATIENTS

We use a central estimate of 2.5 days based on the median reported by Innes et al. (2005). This figure relates to all patients in the low risk category, including those that were unable to tolerate oral antibiotics and were switched to the same care as the high risk group at an early stage.

3.3.3. COST OF HOSPITALISATION

We use the mean number of bed days (8.5) and multiply this by the daily hospitalisation cost of £243 for an acute adult bed-day from NHS reference costs (Curtis and Netten 2006). This gives a total of £2065.5. Using the lower estimate of 5 days gives a total of £1215.

3.4. COST OF ANTIBIOTICS

3.4.1. COST OF INTRAVENOUS/INPATIENT ANTIBIOTICS

The NCCN guidelines on prevention & treatment of cancer-related infections (2007) state that FN can be treated with any of the following intravenous antibiotic regimens:-

- an antibiotic monotherapy (imipenem with cilastatin, or meropenem, or cefepime or ceftazidime, or piperacillin with tazobactam), or
- a combination therapy (an aminoglycoside plus an antipseudomonal penicillin, or ciprofloxacin plus an antipseudomonal penicillin, or an aminoglycoside plus an antipseudomonal cephalosporin (cefepime or ceftazidime)), or
- one of the above plus vancomycin.

Table 6 shows a range of these alternative antibiotic treatments, together with their dosages and acquisition costs, taken from the BNF. This list is not completely exhaustive (for example, there are other amino glycosides). The cost depends on treatment duration. As discussed above, the NCCN guidance advises treatment until the neutrophil count (ANC) recovers, or for 7-14 days for specific infections (or occasionally up to 21 days). However, the mean length of stay (discussed above) has been estimated as 8.5 days; therefore, a length of treatment of 8.5 days has been used here. Based on this length of treatment, and depending on the type of antibiotic used,

the antibiotic acquisition costs range from £221.85 to £769.28. The mean cost across these antibiotic regimens is £59.64 per day, or £506.94 for 8.5 days.

Around 10% of patients report having a penicillin allergy (although only around 1% actually do) (Solensky, 2003). If it is assumed that 90% of patients receive the cheapest combination treatment (gentamicin + ticarcillin), and that the 10% who report a penicillin allergy receive gentamicin + ceftazidime, the average cost can be estimated as (0.9 x £27.73) + (0.1 x £48.60) = £29.82 per day, or £253.47 for 8.5 days. The administration cost is assumed to be included in the cost per bed day and has not been added separately.

3.4.2. COST OF ORAL/OUTPATIENT ANTIBIOTICS

The NCCN guidelines state that for FN patients at low risk of complications, oral antibiotics may be given, e.g. ciprofloxacin plus amoxicillin/clavulanate (or ciprofloxacin plus clindamycin for penicillin-allergic patients), and patients may be treated as outpatients. These drugs and their costs, taken from the BNF, are shown in Table 7. Since the NCCN guidelines state that antibiotics are often given for 7-14 days, an average length of treatment of 10.5 days is assumed. Assuming that 90% patients receive the cheapest combination and the 10% reporting a penicillin allergy receive the other combination, the average cost can be estimated as (0.9 x £1.25) + (0.1 x £7.95) = £1.92 per day, or £20.15 for 10.5 days.

We also assume that the cost of an outpatient visit is relevant to these patients, costed at £87 (2007-8 Outpatient NHS Tariff, specialty code 370, Adult follow up attendance, medical oncology).

Table 6: Intravenous antibiotics: acquisition costs per FN episode

Treatment	Component	Dosage/ day (mg)	Cost per vial/ unit	Cost/ day	Total cost/ day	Days/ episode	Total cost/ episode
Monotherapy							
IV ceftazidime	Ceftazidime	3-6g/d; assume 4.5g/d	£17.90 for 2g	£40.28	**£40.28**	8.5	**£342.38**
IV imipenem with cilastatin	Imipenem with cilastatin	1-2g/d or up to 4g/d; assume 2g/d	£12 for 0.5g	£48.00	**£48.00**	8.5	**£408.00**
IV piperacillin with tazobactam	Piperacillin with tazobactam	4.5g every 6h = 18g/d	£15.79 for 4.5g	£63.16	**£63.16**	8.5	**£536.86**
Combination therapy							
IV gentamicin (aminoglycoside) + ticarcillin (antipseudomonal penicillin)	Gentamicin	5-7 mg/kg = 450mg/d	£1.48 for 80mg	£8.33	**£27.73**	8.5	**£235.71**
	Ticarcillin	3.2g every 6-8h = 10.97g/d	£5.66 for 3.2g	£19.41			
IV amikacin (aminoglycoside) + piperacillin with tazobactam (antipseudomonal penicillin)	Amikacin	15-22.5mg/kg daily = 1406mg/d	£10.14 for 500mg	£28.52	**£91.68**	8.5	**£779.28**
	Piperacillin with tazobactam	4.5g every 6h = 18g/d	£15.79 for 4.5g	£63.16			
IV ciprofloxacin + ticarcillin (antipseudomonal penicillin)	Ciprofloxacin	200-400mg twice daily = 600mg daily	£22 for 400mg	£33.00	**£52.41**	8.5	**£445.49**
	Ticarcillin	3.2g every 6-8h = 10.97g/d	£5.66 for 3.2g	£19.41			
IV ciprofloxacin + piperacillin with tazobactam (antipseudomonal penicillin)	Ciprofloxacin	200-400mg twice daily = 600mg daily	£22 for 400mg	£33.00	**£96.16**	8.5	**£817.36**
	Piperacillin with tazobactam	4.5g every 6h = 18g/d	£15.79 for 4.5g	£63.16			
IV gentamicin (aminoglycoside) + ceftazidime	Gentamicin	5-7 mg/kg = 450mg/d	£1.48 for 80mg	£8.33	**£48.60**	8.5	**£413.10**
	Ceftazidime	3-6g/d; assume 4.5g/d	£17.90 for 2g	£40.28			
IV amikacin (aminoglycoside) + ceftazidime	Amikacin	15-22.5mg/kg daily = 1.406g/d	£10.14 for 0.5g	£28.52	**£68.79**	8.5	**£584.72**
	Ceftazidime	3-6g/d; assume 4.5g/d	£17.90 for 2g	£40.28			
Mean costs across regimens					**£59.64**		**£506.94**
Average cost for 90% gentamicin + ticarcillin and 10% gentamicin + ceftazidime (penicillin allergy)					**£29.82**		**£238.54**

Table 7: Oral antibiotics: acquisition costs per FN episode

Treatment	Component	Dosage/ day (mg)	Cost per vial/ unit	Cost/ day	Total cost/ day	Days/ episode	Total cost/ episode
Ciprofloxacin plus amoxicillin/clavulanate	Ciprofloxacin	250-750mg twice daily = approx 1g/d	£2.77 for 20 tablets of 0.5g	£0.28	**£1.25**	10.5	**£13.11**
	Amoxicillin/clavulanate	250mg every 8h = 750mg/d	£6.80 for 21 tablets of 250g	£0.97			
Ciprofloxacin plus clindamycin (for penicillin-allergic patients)	Ciprofloxacin	250-750mg twice daily = around 1g/d	£2.77 for 20 tablets of 0.5g	£0.28	**£7.95**	10.5	**£83.51**
	Clindamycin	150-450mg every 6h = approx 1200mg/d	£23.03 for 24 tablets of 150mg	£7.68			
Average cost assuming 10% reported allergy to penicillin					**£1.92**		**£20.15**

3.5. SUMMARY OF COSTS

Table 8: Cost per patient treated as inpatient

Cost per day in hospital	243
Number of days in hospital	8.5
Cost per day of antibiotics	59.64
Number of days of antibiotics	8.5
Total	**2572.44**

Table 9: Cost per patient treated with oral antibiotics

Cost per day in hospital	243
Number of days in hospital	2.5
Cost per day of antibiotic	1.92
Number of days of antibiotic	10.5
Outpatient visit	87
Total	**714.66**

The overall cost per episode of FN is the average of the cost per patient treated as an inpatient (84.6%)(Table 8) and the cost per patient treated with oral antibiotics and early hospital discharge (15.4%)(Table 9). Total mean cost = £2286

If the lowest cost IV antibiotics are used this estimate falls to £2072.
If the duration of inpatient stays is 5 days in place of 8.5 the estimate falls to £1390.
If both the lowest cost IV antibiotics are used and the duration of inpatient stay is 5 days, the estimate falls to £1264.

By means of comparison, the 2006 reference cost (HRG S07 – using the same HRG code as considered appropriate by the ERG group (see page 47)) is £1782. The national tariff cost for 2007/2008 is £2169.
Using the Roche HRG code D25, the 2005/6 reference cost is £2,072. The 2007/8 tariff cost (used by Roche) is £3,003.
The difference in these codings and consequent costs appears to be the result of a different approach to identifying the appropriate ICD code. The Roche HRG appears to be derived from the ICD code C34 which is appropriate to lung cancer (Malignant neoplasm of bronchus and lung, source: WHO ICD version 2007) which in turn maps to HRG code D25. However, this fails to consider the actual cost of treatment for febrile neutropenia.

The ERG approach focuses instead on febrile neutropenia. The appropriate ICD code here is D70 (drug induced neutropenia) which in turn maps to HRG code S08. HRG code S07 is more appropriate than SO8 since they are identical except for the inclusion in the former of additional chronic conditions (Other Haematological or Splenic Disorders w cc) and consequent higher costs.

4. COST EFFECTIVENESS RESULTS

The base case parameter values based on the evidence identified in this report are as follows:

	DSU base case	***Roche***
The probability that a patient experiences at least one episode of FN	5.95	6.5% to 10%
Number of FN events	1.4	2.4
Cost per FN event	£2286	£4781

Table 10: Sensitivity analysis of cost effectiveness for erlotinib for the treatment of NSCLC

	Parameter values			Effects of parameter changes		Revised results		
	Risk of FN	Events per affected patient	Cost per event	Change to Incremental cost	Change to Incremental QALYs	Incremental cost	Incremental QALYs	ICER
	1.80%	1	£1,264	+£105.40	-0.00073	£1,051.33	0.01742	£60,342
	4.22%	1	£1,264	+£82.95	-0.00003	£1,028.88	0.01813	£56,758
	5.95%	1	£1,264	+£66.91	+0.00047	£1,012.84	0.01863	£54,362
	8.31%	1	£1,264	+£45.02	+0.00116	£990.95	0.01932	£51,296
	1.80%	1.4	£1,264	+£98.72	-0.00052	£1,044.65	0.01763	£59,246
	4.22%	1.4	£1,264	+£67.30	+0.00046	£1,013.23	0.01862	£54,419
	5.95%	1.4	£1,264	+£44.84	+0.00117	£990.77	0.01932	£51,270
	8.31%	1.4	£1,264	+£14.20	+0.00213	£960.13	0.02029	£47,328
	1.80%	2.4	£1,264	+£82.03	-0.00000	£1,027.96	0.01816	£56,616
	4.22%	2.4	£1,264	+£28.16	+0.00169	£974.09	0.01985	£49,078
	5.95%	2.4	£1,264	-£10.34	+0.00290	£935.59	0.02106	£44,431
	8.31%	2.4	£1,264	-£62.87	+0.00455	£883.06	0.02271	£38,890
	1.80%	1	£2,286	+£91.90	-0.00073	£1,037.83	0.01742	£59,568
	4.22%	1	£2,286	+£51.31	-0.00003	£997.24	0.01813	£55,013
	5.95%	1	£2,286	+£22.30	+0.00047	£968.23	0.01863	£51,968
	8.31%	1	£2,286	-£17.29	+0.00116	£928.64	0.01932	£48,070
	1.80%	1.4	£2,286	+£79.82	-0.00052	£1,025.75	0.01763	£58,174
	4.22%	1.4	£2,286	+£23.00	+0.00046	£968.93	0.01862	£52,040
DSU preferred values	**5.95%**	**1.4**	**£2,286**	**-£17.62**	**+0.00117**	**£928.31**	**0.01932**	**£48,038**
	8.31%	1.4	£2,286	-£73.04	+0.00213	£872.89	0.02029	£43,028
	1.80%	2.4	£2,286	+£49.63	-0.00000	£995.56	0.01816	£54,832
	4.22%	2.4	£2,286	-£47.78	+0.00169	£898.15	0.01985	£45,252
	5.95%	2.4	£2,286	-£117.41	+0.00290	£828.51	0.02106	£39,346
	8.31%	2.4	£2,286	-£212.41	+0.00455	£733.52	0.02271	£32,304
	1.80%	1	£3,852	+£71.22	-0.00073	£1,017.15	0.01742	£58,381
	4.22%	1	£3,852	+£2.83	-0.00003	£948.76	0.01813	£52,338
	5.95%	1	£3,852	-£46.07	+0.00047	£899.86	0.01863	£48,299
	8.31%	1	£3,852	-£112.76	+0.00116	£833.17	0.01932	£43,128
	1.80%	1.4	£3,852	+£50.87	-0.00052	£996.80	0.01763	£56,532
	4.22%	1.4	£3,852	-£44.88	+0.00046	£901.05	0.01862	£48,394
	5.95%	1.4	£3,852	-£113.33	+0.00117	£832.60	0.01932	£43,086
	8.31%	1.4	£3,852	-£206.70	+0.00213	£739.23	0.02029	£36,439
ERG report results	**1.80%**	**2.4**	**£3,852**	**+£0.00**	**+0.00000**	**£945.93**	**0.01816**	**£52,098**
	4.22%	2.4	£3,852	-£164.14	+0.00169	£781.79	0.01985	£39,389
	5.95%	2.4	£3,852	-£281.48	+0.00290	£664.45	0.02106	£31,555
	8.31%	2.4	£3,852	-£441.56	+0.00455	£504.37	0.02271	£22,213

Table 10 shows the cost effectiveness results using the DSU preferred values and a range of sensitivity analyses based on these figures and those submitted by Roche. These results were calculated by the ERG (LRiG).

Using the DSU base case values, the ICER is £48k. Using the 95% confidence interval around the central estimate of the probability a patient experiences a FN event as upper and lower bounds yields ICERs of £43k and £52k respectively.

If the central estimate of the probability of FN is combined with a higher number of FN events and a higher cost per episode (both as in the original Roche submission) the ICER is £32k.

5. REFERENCES

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6. APPENDICES

Appendix 1 – Search strategies for incidence of Febrile Neutropenia with docetaxel treatment

Search strategy for Medline and Cochrane Databases

1. Carcinoma, Non-Small-Cell Lung/
2. Lung neoplasms/
3. docetax?l.tw.
4. docetax?l.rn.
5. docetax?l.nm.
6. taxotere.mp.
7. 1 or 2
8. or/3-6
9. 7 and 8

Search strategy for EMBASE

1. Lung non Small Cell Cancer/
2. Lung cancer/
3. docetax?l.tw.
4. docetax?l.rn.
5. docetax?l.nm.
6. taxotere.mp.
7. 1 or 2
8. or/3-6
9. 7 and 8
10. neutropen$.tw.
11. neutropaen$.tw.
12. 9 and 12