



## Research paper

# The burden of neutropenic sepsis in patients with advanced non-small cell lung cancer treated with single-agent docetaxel: A retrospective study



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## ABSTRACT

**Objectives:** To describe rates of confirmed and suspected neutropenic sepsis (NS) and associated hospital resource utilisation in patients with non-small cell lung cancer (NSCLC) treated with docetaxel monotherapy following relapse after  $\geq 1$  line of chemotherapy in routine UK clinical practice.

**Materials and methods:** A multi-centre, retrospective, observational research study was conducted in seven centres across England and Wales. Adult patients with stage III/IV NSCLC initiated on docetaxel monotherapy between 2010 and 2016 in routine clinical practice (aged  $\geq 18$  years at initiation) following failure of first-line chemotherapy were eligible. Data were collected from hospital medical records between May 2016 and July 2016, on all episodes of confirmed or suspected NS related to docetaxel monotherapy, including patient characteristics. Episodes of confirmed NS were defined as documented absolute neutrophil count  $< 1.0 \times 10^9/L$ , plus temperature  $> 38^\circ C$  or other signs/symptoms of sepsis, otherwise episodes were classified as suspected NS.

**Results:** 121 patients were included (median age 65.5 years; 57.9% male; median 4.0 cycles of docetaxel; 19.8% treated with prophylactic granulocyte-colony stimulating factor). Episodes of confirmed or suspected NS were recorded in 21/121 (17.4%) patients (11 confirmed episodes in 11 [9.1%] patients and 11 suspected episodes in 10 [8.3%] patients). Resource utilisation data were available for 21/22 episodes; the mean length of stay for confirmed NS admissions ( $n = 11$ ) was 9.2 (SD: 9.2) days and for suspected NS admissions ( $n = 10$ ) was 4.7 (SD: 4.6) days. The most commonly prescribed treatment for NS was piperacillin/tazobactam therapy (46.5% of all documented treatments). The mean total costs of managing patients with confirmed NS ( $n = 11$ ) and suspected NS ( $n = 9$ ) were £3163 (SD: £2921) and £1790 (SD: £1585) per patient, respectively.

**Conclusion:** Rates of confirmed NS in UK clinical practice were broadly similar to those reported in clinical trials; however, the burden of suspected NS, not routinely reported elsewhere, is also substantial.

## 1. Introduction

The recommended first-line treatment for the majority of patients

with advanced non-small cell lung cancer (NSCLC) is a platinum-based chemotherapy regimen. Docetaxel monotherapy was the accepted standard of care for more than a decade for second-line therapy in

**Abbreviations:** ANC, absolute neutrophil count; CI, confidence interval; GAFREC, Governance Arrangements for Research Ethics Committees; G-CSF, granulocyte colony stimulating factor; IQR, interquartile range; LOS, length of stay; NICE, National Institute for Health and Care Excellence; NS, neutropenic sepsis; NSCLC, non-small cell lung cancer; SD, standard deviation

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unselected patients with NSCLC relapsing after first-line therapy [1,2]. However, docetaxel is associated with numerous haematological and non-haematological adverse events, including diarrhoea, nausea, vomiting, anaemia, neutropenia and neutropenic sepsis (NS; also known as febrile neutropenia) [3]. Although docetaxel monotherapy remains the benchmark by which other second-line treatments are evaluated, a number of newer therapies for NSCLC have demonstrated benefit in terms of endpoints such as progression-free survival, overall survival and toxicity when used either alone or in combination [2,4,5].

NS is a serious and life-threatening complication of chemotherapy requiring urgent intervention. Therefore all patients presenting with confirmed or suspected NS are treated as a medical emergency with empiric broad-spectrum antibiotic therapy; ongoing treatment is dependent upon the assessment of risk for developing septic complications [6–8]. A meta-analysis of randomised controlled trial data reported the incidence of confirmed NS in patients with NSCLC treated with docetaxel monotherapy as 5.95% (95% CI: 4.22–8.31) [9]. However, there are limited data on the incidence of confirmed and suspected episodes of NS in patients with NSCLC treated with docetaxel monotherapy in the real world clinical setting [10]. It remains unclear what the true burden of confirmed and suspected episodes of NS following docetaxel monotherapy is in patients with NSCLC and what associated healthcare resources are required for their management.

The primary objective of this study was to describe the rate of NS in patients with NSCLC treated with docetaxel monotherapy following relapse after first-line therapy in a ‘real world’ UK clinical practice setting. Other study objectives were to describe the rate of suspected NS, and the NHS resource utilisation and healthcare system cost burden associated with management of patients with NSCLC presenting with confirmed or suspected NS.

## 2. Materials and methods

### 2.1. Study design and setting

This study was a multi-centre, retrospective, observational research study of patients with NSCLC treated with docetaxel monotherapy following failure of first-line therapy. It was conducted in seven secondary or tertiary care centres in England and Wales (ClinicalTrials.gov reference NCT02658747). Centres routinely treating NSCLC patients with docetaxel monotherapy following relapse after first-line chemotherapy, and where patients were likely to present to the same Trust for management of docetaxel-related toxicities were selected. Data were collected between May 2016 and July 2016. This study is reported according to the STROBE (strengthening the reporting of observational studies in epidemiology) statement [11].

### 2.2. Patient selection

Adult patients with stage III or IV NSCLC initiated on docetaxel monotherapy (aged  $\geq 18$  years at initiation) after progression or intolerance to at least one line of prior chemotherapy who were initiated on docetaxel  $\leq 6$  years prior to data collection and who received the last dose of docetaxel  $\geq 30$  days prior to data collection were eligible for inclusion. Patients receiving docetaxel monotherapy as part of a clinical trial and those with no data on absolute neutrophil count (ANC) were excluded from the study. Sequential patients were identified from chemotherapy prescribing data and eligible patients selected in reverse chronological order of docetaxel monotherapy initiation until the target sample size had been reached (with a maximum of 25 patients at each centre) to minimise bias in selecting patients and ensure that data collected reflected recent clinical practice. Data were collected from patients’ medical records by the clinical care team and therefore under the Governance Arrangements for Research Ethics Committees (GAFREC, 2012) research ethics committee approval and patient consent were not required [12].

### 2.3. Outcome measures and definitions

The primary outcome measure was the proportion of patients with a confirmed episode of NS at presentation. There are a variety of NS definitions used in guidelines and clinical protocols [6,8,13,14]. Consistent with the variability in international guidelines, a UK national audit of clinical protocols identified local variations in the definition of neutropenic sepsis; 67% of protocols used a cut-off point for ANC of  $< 1.0 \times 10^9/L$ , 89% of protocols specified temperature cut-off points that included either one or two temperature recordings  $> 38.0^\circ C$ , and 71% of protocols indicated that clinical signs of sepsis should also be considered [13]. To ensure consistency between centres, episodes of NS recorded in patients’ medical records for which treatment was initiated were classified as confirmed NS if the recorded ANC at presentation was  $< 1.0 \times 10^9/L$ , and the recorded temperature was  $> 38^\circ C$  or other signs and symptoms consistent with clinically significant sepsis were documented. All other episodes of NS for which treatment was initiated that did not meet the criteria for confirmed NS at presentation (e.g. episodes where treatment was initiated based only upon an ANC below the cut-off point, or where treatment was initiated based upon temperature above the cut-point and/or clinical suspicion of sepsis with no ANC below the cut-off point) were classified as clinically suspected NS.

Secondary outcome measures included: the distribution of all haematological toxicities (NS, anaemia, thrombocytopenia, neutropenia, pancytopenia); the proportion of patients with an episode of NS when defined as an absolute neutrophil count of  $< 0.5 \times 10^9/L$  and either a temperature  $> 38^\circ C$  or other signs/symptoms consistent with clinically significant sepsis; the proportion of patients experiencing one or more episodes of confirmed or clinically suspected NS; and hospital resource use associated with management of confirmed or clinically suspected NS (including hospital attendances and admissions, investigations and treatment).

### 2.4. Data collection

Data were collected on patient demographic and clinical characteristics at docetaxel initiation (including age, sex, disease history, docetaxel dosing, prophylactic granulocyte colony stimulating factor [G-CSF] treatment) and details of all episodes of confirmed or suspected NS (including details of ANC, temperature and documentation of clinical signs and symptoms of NS at the time of presentation; NS-related attendances/admissions and length of stay [LOS]; NS-related treatment and investigations). Data on episodes of confirmed or suspected NS were collected from the date of initiation of docetaxel monotherapy until 30 days after the end of docetaxel treatment unless patients were hospitalised for docetaxel-related toxicity for longer than 30 days after docetaxel discontinuation in which case data were collected until the date of discharge or death (whichever was sooner).

### 2.5. Cost analysis

A monetary value (UK GBP) was assigned to the following resources: hospital attendances/admissions, antibiotic and G-CSF prescribing. The costs of prescribed medicines were calculated using unit costs published in the British National Formulary volume 71 [15]. Costs for hospital admissions/attendances were calculated based on the ward description for the admission or type of attendance using unit costs published in the NHS National Tariff Payment System [16] and NHS Reference Costs [17]. Mean costs of managing NS were compared with previously reported studies after adjusting for currency and inflation using the Campbell and Cochrane Economics Methods Group and Evidence for Policy and Practice Information and Co-ordination Centre Cost Converter [18].

## 2.6. Statistical analyses

As this was a single cohort, retrospective, observational study no formal sample size calculation was carried out. However, based on an anticipated incidence of confirmed or suspected NS of between 10% and 20%, the estimated 95% confidence intervals (95% CI) for sample sizes of 100, 120 and 150 did not differ greatly and increasing the sample size to 500 patients provided only a marginal decrease in the estimated range of the 95% CI. Therefore, it was considered that a sample size of 500 would not provide a sufficient increase in statistical robustness to warrant the significant additional investment required; a sample size of 120 patients was considered sufficient to provide a reliable estimate of the rate of NS in patients with NSCLC treated with docetaxel monotherapy following failure of first-line therapy.

Data were analysed using descriptive statistics. Quantitative variables are presented as median (interquartile range [IQR] or range) or mean (with standard deviation [SD]). Categorical variables are presented as number (%); rates of NS are also reported with 95% CI (as per the binomial distribution). Data were analysed using only the available data; the denominator is reported for all analyses where data were missing. Data were analysed using Stata V14 (StataCorp).

## 3. Results

The study included 121 patients (median age 65.5 years; 57.9% male) initiated on docetaxel monotherapy between 2010 and 2016. Patient demographic and clinical characteristics are presented in

**Table 1**  
Patient demographic and clinical characteristics.

Overall patient population (n = 121)	
Age at docetaxel initiation (years) <sup>a</sup>	65.5 (57.7–71.2)
Male <sup>b</sup>	70 (57.9%)
Prior NSCLC-related treatments <sup>b</sup>	
1	36 (29.8%)
2	54 (44.6%)
3	22 (18.2%)
4	9 (7.4%)
Prior chemotherapy <sup>b</sup>	
1st-line chemotherapy	71 (58.7%)
2nd-line chemotherapy	39 (32.2%)
3rd-line chemotherapy	1 (0.8%)
Other <sup>c</sup> chemotherapy	10 (8.3%)
Planned cycles of docetaxel <sup>b</sup>	
1	0 (0.0%)
2	1 (0.8%)
3	3 (2.5%)
4	37 (30.6%)
5	3 (2.5%)
6	53 (43.8%)
Not known	24 (19.8%)
Administered cycles of docetaxel <sup>b</sup>	
1	17 (14.0%)
2	18 (14.9%)
3	19 (15.7%)
4	37 (30.6%)
5	6 (5.0%)
6	20 (16.5%)
≥7	4 (3.3%)
Docetaxel dose at initiation <sup>b</sup>	
75 mg/m <sup>2</sup>	89 (73.6%)
60 mg/m <sup>2</sup>	27 (22.3%)
Other	5 (4.1%)
Prophylactic G-CSF <sup>b</sup>	24 (19.8%)

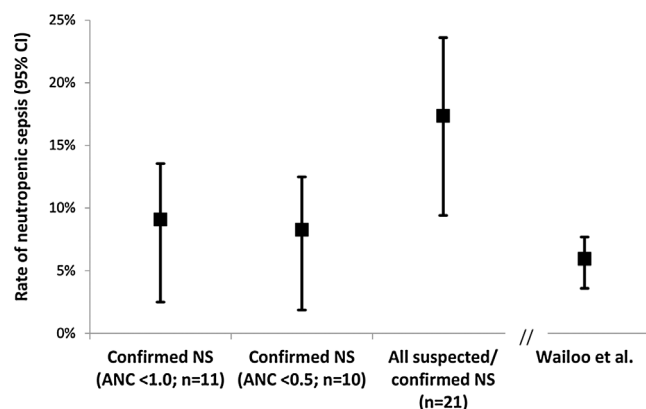
Data presented as <sup>a</sup>median (IQR) or <sup>b</sup>n (%; where % do not sum to 100% this is due to rounding); <sup>c</sup>other chemotherapy includes: chemoradiotherapy (n = 7); adjuvant chemotherapy (n = 2), maintenance chemotherapy (n = 1); NSCLC: non-small cell lung cancer; G-CSF: granulocyte-colony stimulating factor.

**Table 1.** Patients received a median of 2 (IQR: 1–3) NSCLC-related treatments prior to docetaxel monotherapy initiation, with 111 (91.7%) patients receiving ≥1 line of chemotherapy and 10 (8.3%) patients receiving other chemotherapy treatments (chemo-radiotherapy, adjuvant chemotherapy and maintenance chemotherapy; **Table 1**). Patients received a median of 4.0 (IQR: 2.0–4.0) cycles of docetaxel; 89 (73.6%) patients received a dose of docetaxel of 75 mg/m<sup>2</sup> at the first cycle. Treatment with prophylactic G-CSF was recorded in 19.8% of patients (median of 3 [IQR: 1–5] courses per patient; mean duration of 24.0 [SD: 16.5] days). Use of prophylactic G-CSF and starting dose of docetaxel varied between centres; at one centre 100% of patients were treated with prophylactic G-CSF and 71.4% of patients were initiated on 60 mg/m<sup>2</sup> docetaxel, whereas fewer than 15% of patients were treated with prophylactic G-CSF and fewer than 22% of patients were initiated on 60 mg/m<sup>2</sup> docetaxel at the other centres (see Supplemental table S1).

Overall, 80 episodes of docetaxel-related haematological toxicity were recorded in 63 (52.1%) patients (see Supplemental table S2); of these, 22 were episodes of confirmed or suspected NS recorded in 21/121 (17.4% [95% CI: 11.1%–25.3%]) patients. Using an ANC cut-point of  $< 1.0 \times 10^9/L$ , 11 episodes of confirmed NS were identified in 11 (9.1% [95% CI: 4.6%–15.7%]) patients and a further 11 episodes of suspected NS were identified in 10 (8.3% [95% CI: 4.0%–14.7%]) patients (see **Fig. 1**). Using an ANC cut-point of  $< 0.5 \times 10^9/L$  to define NS, 10 (8.3% [95% CI: 4.0%–14.7%]) patients had confirmed NS at presentation (**Fig. 1**). None of the patients treated with prophylactic G-CSF experienced an episode of confirmed or suspected NS.

Of the 22 episodes of confirmed or suspected NS recorded, 21 involved unplanned inpatient admissions and 1 involved a hospitalisation of unknown type. The mean LOS for all NS-related unplanned admissions was 7.0 [SD: 7.5] days per episode. The mean LOS for unplanned admissions for episodes of confirmed NS (n = 11) was 9.2 (SD: 9.2) days and for episodes of suspected NS (n = 10) was 4.7 (SD: 4.6) days. The treatment for NS was recorded for 21/22 confirmed or suspected episodes; a total of 43 courses of treatment were recorded, including 36 courses of antibiotics (most commonly piperacillin/tazobactam therapy) and 4 courses of G-CSF (see Supplemental Table S3). The investigations carried out in relation to episodes of confirmed or suspected NS included 35 radiological investigations (the majority were X-ray investigations) and 78 laboratory investigations (see **Table 2**).

The costs associated with treating patients with confirmed or suspected NS are summarised in **Fig. 2**. The mean total cost of managing confirmed or suspected NS (n = 20 patients with known resource utilisation) was £2545 (SD: £2458) per patient (**Fig. 2**, panel A); mean medication costs were £312 [SD: £224] per patient and mean



**Fig. 1.** Rates of neutropenic sepsis. Confirmed neutropenic sepsis (NS) defined by an absolute neutrophil count (ANC) at presentation of either  $< 1.0 \times 10^9/L$  or  $< 0.5 \times 10^9/L$  and temperature of  $> 38^\circ C$  or other clinical signs/symptoms of sepsis. Estimated rates of NS from a meta-analysis of randomised controlled trial data reported by Wailoo et al. [9] presented for reference.

**Table 2**

Hospital resource use associated with treatment of confirmed or suspected neutropenic sepsis.

Hospital resource	Confirmed or suspected NS (n = 22 episodes)
Hospital admissions <sup>a</sup>	
Unplanned inpatient admissions	21 (95.5%)
Unknown type	1 (4.5%)
Duration of inpatient admissions (days) <sup>b</sup>	
Confirmed and suspected NS	7.0 (SD: 7.5)
Confirmed NS	9.2 (SD: 9.2)
Suspected NS	4.7 (SD: 4.6)
Total radiological investigations <sup>c</sup>	
X-ray	25
CT scan	9
Ultrasound	1
Total laboratory investigations <sup>c</sup>	
Liver function test	21
Full Blood Count	21
Urea and Electrolytes	21
Clotting screen	9
Other	6

Data presented as <sup>a</sup>n (%), <sup>b</sup>mean (SD) or <sup>c</sup>n; Other laboratory investigations: blood cultures, C-reactive protein, sputum cultures, MRSA (methicillin-resistant *Staphylococcus aureus*) screen, cross-match.

NS: neutropenic sepsis; CT: computed tomography.

hospitalisation costs were £2234 [SD: £2310] per patient (Fig. 2, panel B). The mean total costs of managing patients with confirmed NS (n = 11) and suspected NS (n = 9 patients with known resource utilisation) were £3163 (SD: £2921) per patient and £1790 (SD: £1585) per patient, respectively (Fig. 2, panel A).

#### 4. Discussion

This is the first multi-centre study to report the resource utilisation associated with managing episodes of both confirmed and suspected NS. We found that 9.1% of patients with NSCLC treated with docetaxel monotherapy following relapse after first-line therapy experienced at least one episode of confirmed NS using an ANC cut-point of  $< 1.0 \times 10^9/L$ . Overall, 17.4% of patients experienced at least one episode of confirmed or suspected NS related to docetaxel monotherapy that resulted in hospital admission or attendance. These rates are substantially higher than the rate of confirmed NS of 5.95% previously reported in a meta-analysis of randomised controlled trial data [9], indicating a considerably greater burden of NS on patients and hospital resources in the real world clinical setting. The median age of patients included in this study was similar to the median age of patients in the clinical trials included in the meta-analysis [9]. Although data on performance status and medical comorbidities were not collected in the present study, it seems likely that the higher rate of NS observed in our study reflects treatment of higher risk patients in normal clinical practice than would be included in clinical trials. The group of patients classified with suspected NS form a heterogeneous group. They were all treated for NS but were not recorded as having an ANC of  $< 1.0 \times 10^9/L$  and either a temperature  $> 38^\circ C$  or signs/symptoms of sepsis at the time treatment commenced, either due to the data not being available/recorded or because they did not meet the post-hoc criteria required for confirmed NS. However, based on the available data it seems likely that their attendance and treatment for suspected infection was related to the recent administration of docetaxel chemotherapy, warranting their inclusion in the resource utilisation analyses.

The most commonly recorded treatment for confirmed or suspected NS was piperacillin/tazobactam therapy, which is consistent with National Institute for Health and Care Excellence (NICE) guidance on the initial empiric treatment of suspected NS [6]. All episodes of confirmed or suspected NS involved hospitalisation, although the mean

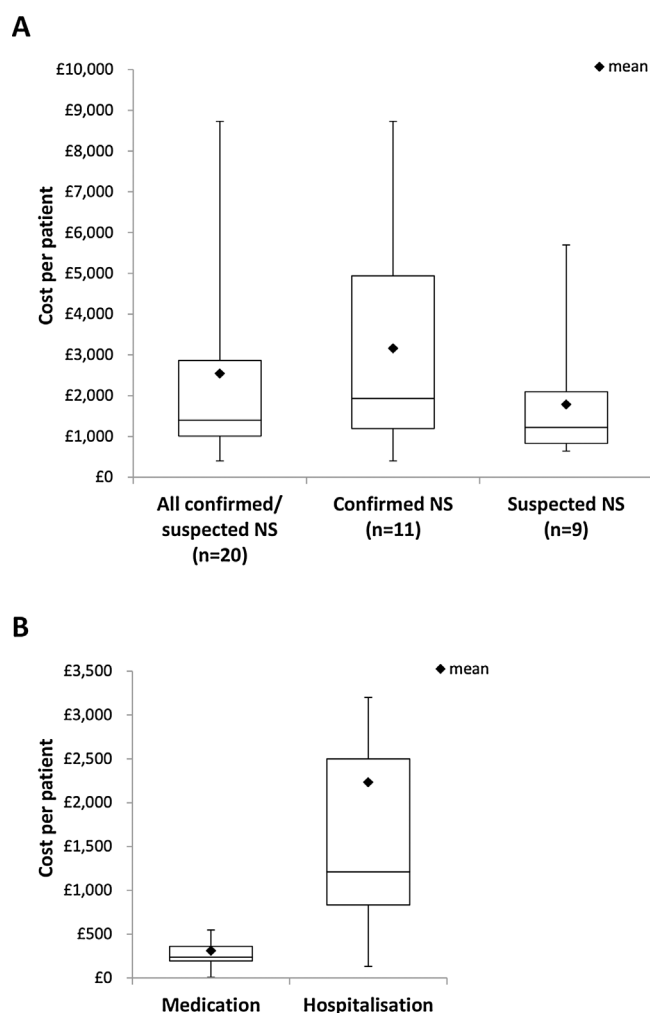


Fig. 2. Cost of managing patients with confirmed or suspected neutropenic sepsis. Panel A: Box plots summarising costs of medication and hospitalisations associated with managing confirmed or suspected neutropenic sepsis (NS). Panel B: Box plots summarising total costs associated with managing confirmed or suspected NS (using absolute neutrophil count  $< 1.0 \times 10^9/L$ ). Box plot whiskers represent range.

LOS for episodes of suspected NS was almost half the LOS for episodes of confirmed NS and this is reflected in the lower resource utilisation costs associated with suspected NS. The mean total cost of hospitalisation and treatment for episodes of confirmed NS was £3163 per patient. These costs are consistent with the costs of treatment and hospitalisation previously reported in patients with NSCLC and febrile neutropenia/leukopenia in a German prospective study (€2975 based on 2005–2007 unit costs [10], equivalent to £3001 in 2016) and in a mixed oncology cohort of patients with NS in a UK single-centre prospective study (£2542 based on 2007 unit costs [19], equivalent to £3013 in 2016). The mean cost of hospitalisation and treatment for episodes of suspected NS was £1790 per patient, highlighting the extent to which the true burden of NS associated with docetaxel monotherapy on hospital resource utilisation is underestimated when only confirmed episodes of NS are considered. This is particularly important considering the lack of consensus for defining NS and emphasizes the importance of clinical judgement in assessing and treating patients for NS in real world clinical practice. Although we used a cut-point for ANC of  $< 1.0 \times 10^9/L$  to define confirmed NS in this study, as this more accurately reflects local NHS protocols [13] and criteria for adverse event reporting [14], only one patient would have been reclassified from confirmed to suspected NS if we had applied a cut-point of  $< 0.5 \times 10^9/L$ .

The routine use of prophylactic G-CSF is not currently



recommended by NICE unless used as an integral part of a prescribed chemotherapy regimen or required for the maintenance of dose intensity [6]. However, we observed considerable variability in prophylactic G-CSF use and starting dose of docetaxel between centres, with all patients at one centre receiving prophylaxis and more than 70% of patients at the same centre receiving a reduced dose of docetaxel at initiation (60 mg/m<sup>2</sup>). It is notable that no patients receiving G-CSF experienced an episode of confirmed or suspected NS, although most patients treated with prophylactic G-CSF were also initiated on a lower dose of docetaxel (60 mg/m<sup>2</sup>) which may also have reduced the risk for NS. Given the changes in the cost of G-CSF due to the availability of a range of biosimilars and the evidence of a beneficial effect in preventing NS [20], our data may lend support for the use of prophylactic G-CSF in this patient group. Although ESMO (European Society for Medical Oncology) guidance suggests use of G-CSF only if the risk of neutropenia exceeds 20% [21], preventing NS is particularly important given the potential longer-term impact on patients that may result from treatment delays, dose reductions or treatment discontinuation as a result of NS. The stress and inconvenience to patients of hospital admission should not be underestimated.

#### 4.1. Strengths and weaknesses

Eligible patients were selected consecutively in reverse chronological order of docetaxel initiation to minimise bias in patient selection and to ensure the results reflect recent clinical practice. The study involved NHS centres from across England and Wales and therefore the result of this study should be generalizable to the wider UK population of patients with NSCLC treated with docetaxel monotherapy after failure of first-line therapy. A uniform definition of confirmed NS was applied to the data from all centres and NS was classified as confirmed or suspected based only on the available data recorded at presentation to ensure consistency between centres. However, as we did not consider assessments recorded in the medical records after initiation of treatment we cannot exclude that some cases of suspected NS may subsequently have been confirmed, leading to an underestimation of the number of episodes of confirmed NS. Data on episodes of NS were collected only from the participating centres; although patients were considered likely to have presented with NS to the treating centre (or to a centre with shared patient record), we cannot exclude that some patients may have presented elsewhere leading to an underestimation of the incidence of NS and associated resource utilisation and costs. Patients with NS may not have presented with a body temperature of > 38 °C due to self-medication with antipyretics; this may have led to an underestimation of the rate of confirmed NS due to the subjective nature of defining clinically significant sepsis in patients without a temperature > 38 °C. The study involved retrospective data collection and evaluation of study outcomes was therefore reliant on the completeness and accuracy of the patients' medical records. The assumptions required when assigning unit costs to the NS-related hospitalisations and treatments may have led to an over- or under-estimation of the true costs of managing episodes of confirmed and suspected NS.

#### 5. Conclusions

The results of this study confirm that NS is a frequent occurrence in patients with NSCLC treated with docetaxel monotherapy in a real world clinical setting. This study also demonstrates that the true burden of NS on patients and healthcare resources is considerably underestimated when episodes of suspected NS are not considered, irrespective of whether an ANC cut-point of < 0.5 × 10<sup>9</sup>/L or < 1.0 × 10<sup>9</sup>/L is used to define confirmed NS. Given the recent rapid increase in the development and availability of novel therapies for NSCLC the role of docetaxel is likely to diminish over time; therefore, the results of this study will be useful for clinicians and their patients when evaluating the risks and benefits of different treatment

options following failure of first-line therapy. These results will also be informative when considering the resource utilisation and costs associated with managing episodes of confirmed and suspected NS in patients with NSCLC.

#### Conflict of interest statement

TT and AD have received honoraria and travel grants from Roche pharmaceuticals; RS is an advisory board member for Roche; JN has received honoraria from Astra Zeneca and Roche and a travel grant from Roche; JL has no conflicts to declare; DT has received fees for consultancy/honoraria from Pierre Fabre, Eli Lilly, Pfizer, Novartis, Astra Zeneca, Celgene, Boehringer Ingelheim, BMS, Roche and contributions to cost of events from Novartis, MSD, Ipsen, Eli Lilly, Roche, BMS; RC was an employee of pH Associates at the time this work was carried out and is currently an employee of QuintilesIMS (Italy); MH, AP, MS are employees of Roche Products Ltd; TN-D has received remuneration for advisory work and educational work on behalf of Roche Products Ltd and support for attending conferences from Roche Products Ltd.

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#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.lungcan.2017.09.014>.

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