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# Adjuvant treatment patterns and outcomes in patients with stage IB-IIIA non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study

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ABSTRACT

*Objectives:* To inform health-technology assessments of new adjuvant treatments, we describe treatment patterns in patients with complete resection of stage IB-IIIA non-small cell lung cancer (NSCLC) in France, Germany, and the United Kingdom (UK).

*Materials and methods:* Data were collected via medical record abstraction. Patients were aged ≥18 years with completely resected stage IB-IIIA NSCLC, diagnosed between 01 January 2009 and 31 December 2011. Median follow-up was 26 months. Adjuvant treatment patterns and clinical outcomes were summarized descriptively.

*Results:* Among the 831 patients studied, 239 (29%) had stage IB disease, 179 (22%) had stage IIA disease, 165 (20%) had stage IIB disease, and 248 (30%) had stage IIIA disease. Adjuvant systemic therapy was received by 402 patients (48.4%), (France, 61.8%; Germany, 51.9%; UK, 33.4%). Use of adjuvant therapy increased with increasing stage of disease. Cisplatin/vinorelbine and carboplatin/vinorelbine were the most frequently

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*Abbreviations:* NSCLC, non-small cell lung cancer; UK, United Kingdom; CI, confidence interval; DFS, disease-free survival; DMFS, distant-metastases-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group; NE, not estimable; ESMO, European Society for Medical Oncology; NICE, National Institute for Health and Care Excellence

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prescribed adjuvant regimens. Median disease-free survival was 48.0 months (95% confidence interval [CI] 42.3–not estimable); the 25th percentile was 13.2 months (95% CI, 11.0–15.3). 204 patients (24%) died during the follow-up period. The median overall survival was not reached, the 25th percentile was 31.2 months (95% CI 26.8–36.0 months). 272 patients (33%) had disease recurrence during the follow-up period. For 86 of those patients, the first recurrence was local or regional with no distant metastasis and 14 had further progression to metastatic disease during the follow-up time. For the other 186 patients, the first recurrence involved distant metastases. A total of 200 patients had metastatic disease at any time during study follow-up.
*Conclusions:* Less than half the patients with stage IB-IIIA NSCLC in this observational study received adjuvant systemic therapy. A high rate of first recurrence with distant metastatic disease was observed, emphasising the need for more effective systemic adjuvant therapies in this population.

## 1. Introduction

Approximately one-third of cases of non-small cell lung cancer (NSCLC) are diagnosed during early stages of the disease and are therefore eligible for surgical resection with curative intent [1]. During surgery, lymph nodes are removed and evaluated histologically. If lymph node metastases are present (and there are no distant metastases), the patient is classified as having stage II or III disease [2].

Adjuvant chemotherapy in early-stage NSCLC is recommended depending on performance status and age but the extent of its use and the agents and combinations used in routine practice are not well documented. Current adjuvant treatments for patients with complete resection of stage IB-IIIA NSCLC have limited efficacy and substantial toxicity [3,4]. There is a clinical need for more efficacious and tolerable therapies in the adjuvant setting, and such interventions are in development [3]. To inform reimbursement bodies and cost-effectiveness evaluations on these upcoming interventions, health-technology assessment agencies will require high-quality data describing current treatment patterns. To our knowledge, few such studies have been conducted in this population.

This observational study aimed primarily at identifying and quantifying the treatment patterns of patients with complete resection of stage IB-IIIA NSCLC in France, Germany, and the United Kingdom (UK). As a second objective, the study aimed at evaluating the disease recurrence and progression for the same patients.

The cost aspects of this study are reported in a back-to-back manuscript in this issue [12].

## 2. Methods

This retrospective observational study (ClinicalTrials.gov identifier: NCT01772225) was conducted among patients with complete resection of stage IB-IIIA NSCLC who were managed by oncologists, pulmonologists, and thoracic surgeons. Candidate study sites were identified using a list of clinical centres known to treat patients with NSCLC for each country. Following an in-depth feasibility enquiry with nine sites (three in each country), study centres were selected with a view to the inclusion of patients and physicians that are representative of the country as a whole with respect to care received (adjuvant and post-progression, including interferon use), while recognising the practicalities of recruiting a sufficient sample for the study. Eligible patients were ≥18 years old with completely resected stage IB-IIIA NSCLC (7th Edition of TNM classification for Lung Cancer Staging) diagnosed between 01 January 2009 and 31 December 2011, had no other cancer treated during follow-up, and had not participated in clinical trials of novel adjuvant therapy. Patients were enrolled through clinical centres using a systematic method for patient sampling to minimise the potential for selection bias.

Study centres in France, Germany, and the UK screened patients for eligibility using medical records of patients who were either living or deceased. Data were extracted at the clinical site via an electronic case report form developed for this study. Data included patient demographic and disease characteristics, secondary and supportive care received, type of adjuvant treatments administered, and resource utilisation. Data on disease recurrence and progression were also assembled for analyses centring on disease-free survival (DFS), distant-metastases-free survival (DMFS), and overall survival (OS).

This study was approved by the following ethics committees:

- UK: National Research Ethics Service Committee Yorkshire and the Humber-Sheffield; date of approval: 12 December 2012
- Germany: Landesärztekammer Hessen; date of approval: 13 December 2012
- France: Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS); date of approval: 19 December 2012
- France: Commission Nationale de l'Informatique et des Libertés (CNIL); date of approval: 25 February 2013

As per the study data management plan, data were omitted from patients whose medical record abstractions were performed incompletely, patients for whom implausible disease progression or treatment dates were reported, patients whose abstracted data were subject to protocol violations, and patients who opted out of the medical record abstraction.

The analysis was descriptive and no hypotheses were formally tested. Results were generated separately for each country and for all countries combined, but no statistical comparisons for results by country were conducted. For time-to-event outcomes (DFS, DMFS, and OS), the number of patients with events and the number censored are presented. Median and 25th percentile times and associated 95% confidence intervals (CIs) were estimated, where possible, using the Kaplan-Meier method for each country and for all countries together. Kaplan-Meier survival curves by country were also plotted for each time-to-event outcome.

Edit and logic checks based on the data collected (e.g., cross-referencing between questions) were conducted and queries resolved, where possible.

## 3. Results

### 3.1. Study sites and patient participation

Thirty-nine study sites participated in the study (France, 14; Germany, 11; UK, 14); 20 sites (53%) were specialist cancer sites, 19 (50%) were teaching hospitals, 9 (24%) were tertiary referral sites, and 4 (11%) were other types of facilities (categories not mutually exclusive). One site did not report facility type. Most sites (32 [84%]) reported treating more than 40 NSCLC patients monthly.

The study sites entered data on 868 patients, out of which 831 (95.7%) had sufficient data to be eligible for analysis (France, 251; Germany, 287; UK, 293). The median follow-up period for all patients was 26 months (France, 30 months; Germany, 24 months; UK, 25 months).

### 3.2. Patient characteristics

Of 831 patients, 62% (513/831) were male, although the proportion ranged from 70.9% in France to 61.0% in Germany and 54.6% in the UK. Overall, 67% (557/831) were aged > 65 years at diagnosis and there were 20–30% of patients in each disease stage. Adenocarcinomas were the most prevalent (53%) followed by squamous cell carcinoma (38%), large cell tumors (2%) and other/unspecified (6%). Overall, 7.7% of patients had participated in clinical trials of post-recurrence treatment (Table 1). A similar proportion of patients were current smokers across the three countries (Table 2).

### 3.3. Adjuvant systemic therapy

Overall, 402 patients (48.4%) received adjuvant systemic therapy (61.8% in France, 51.9% in Germany, and 33.4% in the UK). The use of adjuvant therapy increased with advancing disease stage in all three countries (Table 3).

Overall cisplatin/vinorelbine, the most frequently prescribed adjuvant regimen in all three countries, was given to 258 patients (64.2% of those who received any adjuvant systemic therapy overall) with high heterogeneity between France, Germany, and the UK. Carboplatin/vinorelbine was given to 39 patients (9.7% of those who received any adjuvant systemic therapy overall). Cisplatin/gemcitabine was given to 19 patients (4.7% of those given any adjuvant systemic therapy). Overall, no other adjuvant chemotherapy regimen was given to more than 4% of all patients receiving adjuvant chemotherapy. If we consider data per country, the only other regimens given to more than 4% of patients receiving adjuvant chemotherapy in any country were carboplatin/paclitaxel (given to 8.4% of patients receiving adjuvant chemotherapy in France), carboplatin/pemetrexed (given to 6.0% of patients receiving adjuvant chemotherapy in Germany), cisplatin/pemetrexed (given to 5.2% and 4.7% of patients receiving adjuvant chemotherapy in France and Germany, respectively), and cisplatin alone (given to 5.1% of patients receiving adjuvant chemotherapy in the UK) (see Supplemental Table 1).

The median number of planned and administered cycles was four for cisplatin/vinorelbine and carboplatin/vinorelbine, and 3.5 for cisplatin/gemcitabine. A majority of patients treated with the three most common adjuvant chemotherapy regimens completed their planned course of treatment for both drugs (cisplatin [62.1%]/vinorelbine [66.0%]; carboplatin [64.1%]/vinorelbine [59.0%]; cisplatin [57.9%]/gemcitabine [57.9%]). The proportion of patients receiving adjuvant chemotherapy exclusively in the outpatient setting was greater for those receiving carboplatin/vinorelbine (72%) than for those receiving cisplatin/vinorelbine (55%) or cisplatin/gemcitabine (53%).

Of the 429 (51.6%) patients across the three countries who did not receive adjuvant systemic therapy, reasons included treatment being declined by the patient (12.6%), comorbidities (11.9%), complication or delay in recovery from surgery (8.4%), and poor performance status (7%).

### 3.4. Survival and disease recurrence

Overall, 272 patients (33%) had disease recurrence during the observed follow-up period; however, the results differed by country with disease recurrence ranging from 26% observed in the UK sample to 43% in the French sample (Table 4). For 86 patients (10% of the total; 32% of those with recurrence), the first recurrence was local or regional with no distant metastasis. For the other 186 patients (22% of the total; 68% of those with recurrence), the first recurrence involved distant metastases (60 of whom also had concomitant local or regional recurrence). Among the 86 patients with only local disease at first recurrence, 14 progressed to metastatic disease during the follow-up time observed, so a total of 200 patients had metastatic disease at any time during study follow-up. Heterogeneity was observed across the countries with 11.5% observed in the German sample ranging to 22.7% in the UK for patients with further progression to distant metastases. The most common sites of metastasis (not mutually exclusive) were brain (82 patients; 41%), lung (65 patients; 33%), bone (47 patients; 24%), and liver (26 patients; 13%).

The median OS was not reached during the follow-up time available for analysis. The 25th percentile of estimated OS was 31.2 months (95% confidence interval [CI] 26.8–36.0 months). Overall, 204 patients (24%) were reported to have died; however, the survival analysis included only 201 of these 204 deaths as date of death was not reported for 3 patients (Table 4).

Median DFS was 48.0 months (95% CI, 42.3 months–not estimable); median DFS was 38.5 months in France (95% CI, 27.4–non estimable [NE]), 48.0 months in Germany (95% CI, 48.0 months–NE), and NE in the UK (95% CI, 42.3-NE) (Fig. 1). First quartile DFS appears to be substantially longer for patients with stage IB disease than for those with IIA, IIB, or IIIA disease (Table 5).

Among the 86 patients who had local or regional recurrence without metastases, 43 (50%) received systemic treatment. Heterogeneity was observed across countries with 66% of the French patients receiving systemic treatment, 42% of the German patients, and 32% of the UK patients. Among the 200 patients who experienced distant metastatic disease (whether it represented their first recurrence or progression from a local or regional recurrence), 97 (49%) received systemic

**Table 1**
Patient characteristics at inclusion.

| Characteristic | France (N = 251) n (%) | Germany (N = 287) n (%) | United Kingdom (N = 293) n (%) | Overall (N = 831) n (%) |
|---|---|---|---|---|
| Age in years | | | | |
| ≤ 60 | 110 (43.8) | 98 (34.1) | 66 (22.5) | 274 (33.0) |
| 61–70 | 90 (35.9) | 109 (38.0) | 109 (37.2) | 308 (37.1) |
| ≥ 71 | 51 (20.3) | 80 (27.9) | 118 (40.3) | 249 (30.0) |
| Male | 178 (70.9) | 175 (61.0) | 160 (54.6) | 513 (61.7) |
| Carcinoma type | | | | |
| Adenocarcinoma or bronchioloalveolar | 151 (60.2) | 152 (53.0) | 141 (48.1) | 444 (53.4) |
| Squamous cell | 78 (31.1) | 111 (38.7) | 125 (42.7) | 314 (37.8) |
| Large cell | 8 (3.2) | 7 (2.4) | 5 (1.7) | 20 (2.4) |
| Other or unspecified histology[a] | 14 (5.6) | 17 (5.9) | 22 (7.5) | 53 (6.4) |
| Pathologic disease stage | | | | |
| IB | 58 (23.1) | 70 (24.4) | 111 (37.9) | 239 (28.8) |
| IIA | 39 (15.6) | 57 (19.9) | 83 (28.3) | 179 (21.5) |
| IIB | 46 (18.3) | 64 (22.3) | 55 (18.8) | 165 (19.9) |
| IIIA | 108 (43.0) | 96 (33.4) | 44 (15.0) | 248 (29.8) |
| ECOG performance status[b] | | | | |
| 0 or 1 | 114 (98.3) | 114 (95.8) | 188 (94.0) | 416 (95.6) |
| Karnofsky performance status[c] | | | | |
| 80% to 100% | 0 | 47 (94.0) | 0 | 47 (94.0) |
| Systematic lymph node dissection | 241 (96.0) | 259 (90.2) | 98 (33.4) | 598 (72.0) |
| Comorbidities (categories not mutually exclusive) | | | | |
| Cardiovascular disease | 84 (33.5) | 160 (55.7) | 89 (30.4) | 333 (40.1) |
| Chronic obstructive pulmonary disease or asthma | 50 (19.9) | 89 (31.0) | 76 (25.9) | 215 (25.9) |
| History of cancers other than NSCLC | 35 (13.9) | 27 (9.4) | 29 (9.9) | 91 (11.0) |
| Other or no data available | 192 (76.5) | 210 (73.2) | 209 (71.3) | 611 (73.5) |

ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer.

[a] Other carcinoma type is represented by adenosquamous carcinoma, carcinoma with pleomorphic sarcomatoid or sarcomatous elements, NSCLC not specified, or other.

[b] Reported for 435 patients. At time of surgical resection.

[c] Reported for 50 patients.

**Table 2**
Smoking status.

| Smoking Status | France (N = 251)[a] n (%) | Germany (N = 287)[a] n (%) | United Kingdom (N = 293)[a] n (%) | Overall (N = 831)[a] n (%) |
|---|---|---|---|---|
| Never smoked (less than 100 cigarettes in their life) | 32 (12.7) | 28 (9.8) | 20 (6.8) | 80 (9.6) |
| Permanently stopped smoking before lung cancer was suspected | 108 (43.0) | 90 (31.4) | 140 (47.8) | 338 (40.7) |
| Permanently stopped smoking after lung cancer was suspected and before resection surgery | 38 (15.1) | 30 (10.5) | 31 (10.6) | 99 (11.9) |
| Permanently stopped smoking after resection surgery | 10 (4.0) | 18 (6.3) | 9 (3.1) | 37 (4.5) |
| Current smoker | 52 (20.7) | 82 (28.6) | 69 (23.5) | 203 (24.4) |
| Data not available | 11 (4.4) | 39 (13.6) | 24 (8.2) | 74 (8.9) |

[a] N: Denominator for percentage calculation is number of patients for whom smoking status was reported.

**Table 3**
Percentages of patients receiving adjuvant therapy, by stage.

| Variable | France (N = 251)[a] n (%) | Germany (N = 287)[a] n (%) | United Kingdom (N = 293)[a] n (%) | Overall (N = 831)[a] n (%) |
|---|---|---|---|---|
| **Patients receiving adjuvant chemotherapy** | | | | |
| None | 96 (38.2) | 138 (48.1) | 195 (66.6) | 429 (51.6) |
| **Received adjuvant chemotherapy** | 155 (61.8) | 149 (51.9) | 98 (33.4) | 402 (48.4) |
| Stage IB[b] | 10/58 (17.2) | 12/70 (17.1) | 14/111 (12.6) | 36/239 (15.1) |
| Stage IIA[b] | 22/39 (56.4) | 34/57 (59.6) | 37/83 (44.6) | 93/179 (52.0) |
| Stage IIB[b] | 32/46 (69.6) | 39/64 (60.9) | 25/55 (45.5) | 96/165 (58.2) |
| Stage IIIA[b] | 91/108 (84.3) | 64/96 (66.7) | 22/44 (50.0) | 177/248 (71.4) |

[a] N: Denominator for percentage calculation is the number of patients for whom data were recorded for the respective question.
[b] The number of patients receiving adjuvant chemotherapy in each country was used as the denominator.

treatment. The most commonly prescribed agents to treat distant metastatic disease were pemetrexed (41 patients) and carboplatin (40 patients).

## 4. Discussion

Age and sex distributions of patients in this study are generally consistent with those of the NSCLC population who have undergone complete surgical resection and who are candidates for adjuvant therapy [5]; approximately half were older than 65 years and a majority were male (61.7% overall). Another characteristic of NSCLC populations is the reported smoking rate (current or past) of over 80%. The proportion of current smokers was the highest in Germany (28.6%) and the lowest in France (20.7%). Because smoking behaviour is self-reported, smoking is a known cause of lung cancer [6], and there is a social stigma associated with smoking; these quantitative findings should be interpreted cautiously.

Adenocarcinoma was the most common histology in the study sample (52.7%), followed by squamous cell carcinoma (37.8%). This is consistent with an increasing proportion of patients having adenocarcinoma histology and a decreasing proportion having squamous cell histology over recent years, which has been observed in studies of NSCLC in several European countries, including the UK [7] and France [8]. Performance status, among approximately half of the patients for whom it was reported, was generally good (ECOG 0 or 1), which is consistent with the selection of patients for surgical resection, according to published guidelines [9,10].

The most frequent stage of disease in the study population was IIIA (29.8%), followed by IB (28.8%), IIA (21.5%), and IIB (19.9%). However, stage distribution varied markedly by country. In France, the proportion of patients with stage IIIA was higher (43.0%) than in Germany (33.4%) or the UK (15.0%); the proportion of patients with

**Table 4**
Non-small cell lung cancer progression and death from the medical record abstraction.

| Variable | France (N = 251) n (%) | Germany (N = 287) n (%) | United Kingdom (N = 293) n (%) | Overall (N = 831) n (%) |
|---|---|---|---|---|
| Patients with recurrence | 108 (43.0) | 89 (31.0) | 75 (25.6) | 272 (32.7) |
| Local or regional recurrence only | 38 (35.2) | 26 (29.2) | 22 (29.3) | 86 (31.6) |
| Distant metastases with local or regional recurrence | 21 (19.4) | 21 (23.6) | 18 (24) | 60 (22.1) |
| Distant metastases without local or regional recurrence | 49 (45.4) | 42 (47.2) | 35 (46.7) | 126 (46.3) |
| Further progression to distant metastases (for patients with local/regional recurrence only) | 6 (15.8) | 3 (11.5) | 5 (22.7) | 14 (16.3) |
| Patients deceased | 67 (26.7) | 84 (29.3) | 87 (29.7) | 238 (28.6) |
| Death due to NSCLC or NSCLC complications (or NSCLC could not be ruled out as cause) | 55 (82.1) | 34 (40.5) | 44 (50.6) | 133 (55.9) |
| Death due to other cause(s) | 8 (11.9) | 7 (8.3) | 15 (17.2) | 30 (12.6) |
| Death due to unknown cause | 3 (4.5) | 13 (15.5) | 25 (28.7) | 41 (17.2) |
| Data not available | 1 (1.5) | 30 (35.7) | 3 (3.4) | 34 (14.3) |
| Setting of death | 66 | 54 | 84 | 204 |
| At home | 10 (15.2) | 3 (5.6) | 10 (11.9) | 23 (11.3) |
| In hospital (private hospital in France and Germany) | 4 (6.1) | 0 | 32 (38.1) | 36 (17.6) |
| In public hospital (for France and Germany only) | 42 (63.6) | 23 (42.6) | 0 | 65 (31.9) |
| In a hospice (for Germany and UK only) | 0 | 1 (1.9) | 8 (9.5) | 9 (4.4) |
| Data not available | 10 (15.2) | 27 (50.0) | 34 (40.5) | 71 (34.8) |

NSCLC = non-small cell lung cancer.

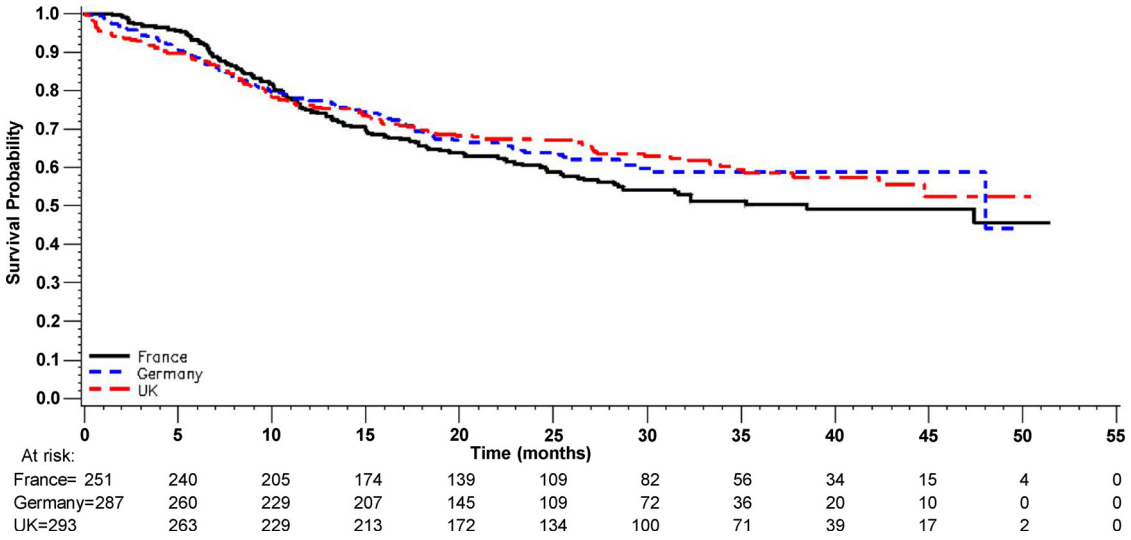


**Fig. 1.** Kaplan-Meier survival curves for disease-free survival, by country UK: United Kingdom.

**Table 5**
Time to event outcomes (time from surgical resection), by stage.

| Variable | Stage I B (N = 239) n (%) | Stage II A (N = 179) n (%) | Stage II B (N = 165) n (%) | Stage III A (N = 248) n (%) | Overall (N = 831) n (%) |
|---|---|---|---|---|---|
| Disease-free survival (DFS) | | | | | |
| Total patients | 239 | 179 | 165 | 248 | 831 |
| Disease recurrence or death | 71 (29.7) | 68 (38.0) | 73 (44.2) | 120 (48.4) | 332 (40.0) |
| Censored | 168 (70.3) | 111 (62.0) | 92 (55.8) | 128 (51.6) | 499 (60.0) |
| 25th percentile of DFS, months (95% CI) | 23.7 (18.6, 33.9) | 11.9 (9.7, 16.8) | 8.7 (6.8, 13.2) | 10.2 (8.5, 13.5) | 13.2 (11.0, 15.3) |
| Median DFS, months (95% CI) | NE (NE, NE) | 42.3 (42.3, NE) | 38.5 (25.2, NE) | 28.5 (23.4, NE) | 48.0 (42.3, NE) |
| Min, max | 0.2, 50.4 | 0.1, 49.6 | 0.4, 51.4 | 0.4, 50.4 | 0.1, 51.4 |
| Distant metastasis-free survival (DMFS) | | | | | |
| Total patients | 238 | 179 | 165 | 248 | 830 |
| Distant metastasis or death | 59 (24.8) | 63 (35.2) | 63 (38.2) | 99 (39.9) | 284 (34.2) |
| Censored | 179 (75.2) | 116 (64.8) | 102 (61.8) | 149 (60.1) | 546 (65.8) |
| 25th percentile of DMFS, months (95% CI) | 31.6 (20.0, NE) | 15.8 (11.3, 23.2) | 15.2 (7.7, 21.2) | 14.8 (10.6, 17.7) | 17.7 (15.2, 19.9) |
| Median DMFS, months (95% CI) | NE (NE, NE) | 42.3 (41.7, NE) | 48.0 (35.1, NE) | 47.4 (30.2, NE) | NE (48.0, NE) |
| Min, max | 0.2, 50.4 | 0.1, 49.6 | 0.4, 51.4 | 0.4, 50.4 | 0.1, 51.4 |
| Overall survival (OS) | | | | | |
| Total patients | 237 | 179 | 165 | 247 | 828 |
| Death | 34 (14.3) | 54 (30.2) | 47 (28.5) | 66 (26.7) | 201 (24.3) |
| Censored | 203 (85.7) | 125 (69.8) | 118 (71.5) | 181 (73.3) | 627 (75.7) |
| 25th percentile of OS, months (95% CI) | NE (NE, NE) | 25.1 (17.8, 32.4) | 22.1 (16.0, 38.6) | 28.2 (20.4, 35.2) | 31.2 (26.8, 36.0) |
| Median OS, months (95% CI) | NE (NE, NE) | 43.2 (40.2, NE) | NE (NE, NE) | NE (NE, NE) | NE (NE, NE) |
| Min, max | 0.2, 50.4 | 0.1, 50.2 | 0.4, 51.4 | 0.4, 50.4 | 0.1, 51.4 |

CI = confidence interval; NE = non estimable.

stage IB was the highest in the UK (37.9%), intermediate in Germany (24.4%), and the lowest in France (23.1%). The less frequent use of systematic lymph node dissection in the UK (33.4%, compared with 96.0% in France and 90.2% in Germany) may have resulted in some "understaging" of the patients in the UK. Possible differential use of positron emission computed tomography could be another reason contributing to this difference. Alternatively, proportionately more patients with higher-stage disease (IIB and IIIA) may have been referred for definitive radiation therapy in the UK than other countries, rather than being treated primarily with surgery; however, we did not collect the information that would be needed to directly assess this assumption.

Adjuvant cisplatin-based doublet chemotherapy is recommended after surgery for stage II and III disease based on 23 randomised trials published from 1992 to 2005 and five meta-analyses [5]. The European Society for Medical Oncology (ESMO) Consensus guidelines recommends a two-drug combination with cisplatin for patients with NSCLC who are to receive adjuvant chemotherapy [11]. Efficacy in stage IB remains controversial; data suggest a survival benefit only in patients with tumours larger than 4 or 5 cm in diameter [11]. The National Institute for Health and Care Excellence (NICE) (2011)

recommended offering postoperative adjuvant chemotherapy to patients with completely resected NSCLC, good performance status, and T1–3 N1–2 M0 disease; the same should be considered for patients with T2–3 N0 M0 NSCLC and tumours greater than 4 cm in diameter.

In our study, more than 40% of the patients with stage II and 28.6% of patients with stage IIIA did not receive adjuvant therapy despite recommendation from the guidelines. Among those patients receiving adjuvant chemotherapy, the observed type adjuvant chemotherapy in our study is generally consistent with published guidelines [9,10]. The proportion of patients given adjuvant chemotherapy was relatively low among those with stage IB disease (15.1%). The overall proportions of patients with higher stages given adjuvant chemotherapy (stage IIA, 52.0%; stage IIB, 58.2%; stage IIIA, 71.4%) indicate that its use is considerably greater within the patient groups for whom evidence more consistently shows a survival benefit. The same trends were observed within each country, although, stage for stage, the use of adjuvant chemotherapy was the greatest in France, intermediate in Germany, and the lowest in the UK. Other common reasons for not using adjuvant chemotherapy were patient declination and presence of comorbidities.

The predominant use of cisplatin/vinorelbine in this study (administered to 66.5% of patients given adjuvant chemotherapy in France, 55.7% in Germany, and 73.5% in the UK) is consistent with published clinical trials of adjuvant chemotherapy in patients with NSCLC [9]. It is not surprising that carboplatin/vinorelbine was the second most frequently prescribed adjuvant chemotherapy regimen, since carboplatin and cisplatin are closely related in terms of their chemical composition and pharmacologic activities, and carboplatin is frequently substituted for cisplatin in standard chemotherapy regimens, particularly in patients with impaired renal function.

Major clinical outcomes in the adjuvant treatment setting (DFS, DMFS, and OS) are time-dependent. Because the present study was primarily designed to assess recent patterns of care and costs among patients eligible to receive adjuvant chemotherapy, the eligible period of diagnosis of NSCLC was restricted and the follow-up time available for analysis was consequently limited. Therefore, information was not complete enough to estimate median OS (or even median DFS in all countries). This limitation and other differences in study populations should be considered while evaluating these results in the context of clinical trials of adjuvant chemotherapy, where typically results are not reported until follow-up is more mature.

Although the OS experience by stage cannot be directly compared with previously published survival estimates [5] and patients did not all receive adjuvant chemotherapy (proportions varied by stage), several observations can be made about the present study. First, OS estimates by stage indicate that survival proportions at the median overall follow-up time (26 months) for each stage are greater than the 5-year OS estimates published by Lim et al. [5].). DFS data should be interpreted with caution as they are expected to be influenced by follow-up patterns and recording of disease recurrence, and these are expected to differ from those used in clinical trials and also to vary among countries. Therefore, it is not possible to draw any conclusions about differences in DFS among countries. Second, there is an apparently “tighter” distribution of OS at the median time of follow-up (26 months) among patients with stages IIA, IIB, and IIIA in the LuCaBIS population than one might expect based on the spread of 5-year survival estimates published by Lim et al. [5]. Without additional subgroup analyses, it is not possible to determine the extent to which this is related to the observation that the proportion of patients receiving adjuvant chemotherapy in the LuCaBIS population increased by increasing stage, thus perhaps obscuring differences that might be observed in a population of patients who had all received adjuvant chemotherapy.

There were several study limitations. The study used a quasi-random sampling method for the selection of patients within study sites. Sites were selected to achieve variation in geographic location, size, and type, but study data may not be perfectly representative of all sites and physicians treating patients with stage IB-IIIA NSCLC across each country. As with all studies that rely on existing medical records, availability of information varied by practice and country and reflects differences in practice patterns, recording practices, and medical norms. External validation of medical record data was not conducted. Nevertheless, we believe that this study makes a useful contribution to the evidence base required for clinical and health economic decision making.

## Conflict(s) of interest

In the past 5 years, Chouaid C. received fees for attending scientific meetings, speaking, organizing research or consulting from AstraZeneca, Boehringer Ingelheim, Hoffman La Roche, Sanofi Aventis, Eli Lilly, Novartis, Amgen, BMS, MSD and the GSK group of companies.

Andreas S. discloses honoraria for advisory boards and lectures from Roche, Boehringer Ingelheim, Pfizer, and the GSK group of companies.

Danson S. reports grants, personal fees, and nonfinancial support from the GSK group of companies during the conduct of the study, grants and non-financial support from the GSK group of companies, Eli Lilly, Bristol Myers Squibb, Boehringer Ingelheim, AstraZeneca, Onco-NX, Incanthera, Genta, Abraxane, Daiichi-Sankyo, Amgen, Bayer, MSD and Morphotek outside the submitted work; and familial relationship (brother-in-law) with an employee of the GSK group of companies.

Obukohwo S. is an employee of the GSK group of companies.

Benjamin L., Ehness R., Dramard-Goasdoue M. and Barth J. were employees of the GSK group of companies; and Benjamin L., Dramard-Goasdoue M., and Ehness R. hold shares and/or restricted shares in the GSK group of companies.

Hoffmann H. reports no conflict of interest.

Potter V. reports receiving fees from the GSK group of companies regarding the set-up of this study in the UK.

Barlesi F. reports no conflict of interest.

Price M., Wolowacz S., Chirila C., Hollis K., Sweeney C. and Kaye *J.* A. report funding from the GSK group of companies to their employer, RTI Health Solutions, during the conduct of the study.

Kontoudis I. was an employee of the GSK group of companies at the time of the study.

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## Contributorship

All authors were involved in the conception and/or the design of the study.

HH, SA, LB, CoC, ChC, SD, KH, IK, VP, MP, CS and SW participated in the collection or generation of the study data.

SA, LB, CoC, ChC, SD, KH, IK, VP, MP, CS and SW conducted the study.

SA, CoC, ChC, SD, KH, IK, MP, CS, SW contributed to the analysis tools.

SA, FB, LB, CoC, ChC, SD, MHDG, KH, JAK, IK, MP, CS, SW were involved in the analyses and/or the interpretation of the data.

OS was involved in the implementation of the study design.

KH led the design and initiation of the project and served as project supervisor throughout.

ChC was lead statistician of the project, wrote the analysis plan, supervised, programmed, and reviewed the SAS output tables, reviewed and provided input for the reporting of the results.

All authors read, reviewed and approved the present manuscript.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.07.042.

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