Cancer Epidemiology 51 (2017) 1–6

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.canceepidemiology.net

Original Research Article

Trends in prescribing systemic treatment and overall survival for non-small cell lung cancer stage IIIB/IV in the Netherlands: 2008–2012

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ARTICLE INFO

Article history:
Received 28 April 2017
Received in revised form 6 July 2017
Accepted 1 August 2017
Available online 28 September 2017

Keywords:
Lung cancer
NSCLC
Systemic treatement
Overall survival
Trends in prescribing
Pharmacoepidemiology

ABSTRACT

Background: The present study aims to give a detailed overview of day-to-day practice in the systemic treatment of NSCLC stage IIIB/IV and its clinical outcomes in six large teaching hospitals in the Netherlands in the period 2008–2012.
Methods: A retrospective observational cohort study was conducted in the Care for Outcome registry. Patients diagnosed with stage IIIB/IV NSCLC were included and drug data were collected. Outcomes included percentage of patients treated with systemic treatment, percentage of different first line treatment options, survival, and number and percentage of switches, dose reductions (<80% of the initial dose), and early discontinuation (<4 cycles). Descriptive analyses were conducted per hospital, year of diagnosis and several patient characteristics. Predictors for early discontinuation were explored in a logistic regression model.
Results: Overall, 47,9% of 2158 patients that were included received systemic treatment and 33,7% of those received second line treatment. Treatment frequencies were different between age categories, disease stage, PS and hospital ($p < 0.001$). Half of the patients received <4 cycles and dose reductions were found for 20% of all patients. Interhospital differences were observed for early discontinuation and the number of switches. PS2-3 was associated with early discontinuation (OR 1.97 ($p = 0,007$). Median survival was not different between hospitals and years of diagnosis.
Discussion: We provided detailed overview of day-to-day systemic treatment of NSCLC for six hospitals that (a) can fuel interhospital discussion to streamline treatment towards best practice and (b) can serve as reference data for follow-up of the adoption of novel systemic treatment options for advanced lung cancer.

1. Introduction

Non-small cell lung cancer (NSCLC) represents 85 percent of all lung cancer diagnoses in The Netherlands [1]. The majority of patients present with locally advanced or metastatic disease at the time of diagnosis [2]. The 1-year survival rate of metastatic non-small cell lung cancer (NSCLC) is only 20% [1]. Palliative treatments that are provided to these patients aim to preserve or improve quality of life, lengthen life or decrease disease burden. Palliation can consist of symptom relief (best supportive care) or systemic treatment targeted at tumour tissue.

There are various drugs available to target tumour tissue including systemic chemotherapy, targeted therapy – tyrosine kinase inhibitors (TKIs) targeting specific genetic phenotypes- and immunotherapy [3]. Although many (inter)national guidelines are available to support treatment decision making, little is known about how these guidelines resonance in day-to-day clinical

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http://dx.doi.org/10.1016/j.canep.2017.08.001

practice in terms of utilization and clinical outcomes. Also, day-to-day clinical practice may well vary from hospital to hospital.

In the context of a Value Based Health Care system, the present study aims to give a detailed overview of day-to-day practice in the systemic treatment of NSCLC stage IIIB/IV and its clinical outcomes in six large teaching hospitals in the Netherlands over a period of five years (2008–2012). Clinical outcomes studied include overall survival, dose-reductions, treatment switches and early treatment discontinuation.

2. Materials and methods

Clinical data were collected from six large teaching hospitals in The Netherlands. These six hospitals work together under the name of Santeon, a Dutch nationwide Hospital Group. Santeon serves more than 12,5% of the Dutch lung cancer patient population. The individual hospitals are: Canisius Wilhelmina Hospital (Nijmegen), Catharina Hospital (Eindhoven), Martini Hospital (Groningen), Medisch Spectrum Twente (Enschede), Onze Lieve Vrouwe Gasthuis (Amsterdam) and St. Antonius Hospital (Nieuwegein/Utrecht). In 2012, Santeon established the Care for Outcome (CfO) registry that includes outcome data from all patients diagnosed with lung and prostate cancer in one of the six hospitals from 2008 onwards. The CfO registry is built on the general Dutch Cancer Registry (managed by the Netherlands Comprehensive Cancer Organisation (IKNL)) and subsequently enriched with clinical data from the hospitals (through extensive medical chart review and norminalisation of data). These clinical data include, amongst others, tumour characteristics, patient co-morbidities, ECOG performance status, treatment planning and clinical outcomes. Trained medical students supervised by a pulmonary physician extracted all items. Parallel to the CfO registry Santeon established the Santeon Farmadatabase that holds all prescribed and dispensed drugs at the individual patient level for all patients receiving care in one of the six hospitals from 2010 onwards. For every prescription the database includes, amongst others, drug name, dosage, date of administration, and administration route. The study has been approved by the local research ethics committee of each individual hospital.

2.1. Patient selection and data collection

From the CfO database we extracted data from all patients that (1) were diagnosed with NSCLC in one of the Santeon hospitals, (2) had clinical stage IIIB or IV (including both patients with and without systemic treatment), and (3) had follow-up data (vitality status) available. Patients were ignored if the hospital of primary treatment was not the hospital of diagnosis. For this selection of patients, we extracted all prescribed and dispensed drug data from individual hospital pharmacy information systems. Because in the time period under study the tyrosine-kinase inhibitor could also be dispensed from community-pharmacies we additionally reviewed all medical charts if one or more prescription were identified in the hospital pharmacy system to gather data about initiation data and duration of treatment.

2.2. Study parameters

From the drug prescription and dispensing data we constructed an overview of systemic treatments for every patient including the type of systemic treatment and whether it was first, second, or further line of treatment. If the start of a subsequent regimen was less than 90 days after the theoretical end date of the first line treatment (based on 3 weeks per cycle), medical charts were reviewed to determine whether the change of treatment was due to ineffectiveness (progression, no regression) or toxicity. Switch to another treatment option more than 90 days after the theoretical end date of the first line treatment and switch to another treatment option due to ineffectiveness was considered next line treatment. Early switch to another treatment due to toxicity was considered the same line of treatment. Additional cycles after a switch due to toxicity were added to the initially administered number of cycles.

2.3. Outcome parameters

Individual patient survival times were calculated as the time difference (in days) between date of diagnosis and date of death (vitality status as known on 31-12-2014). As a proxy for toxicity,

Table 1
Baseline characteristics per hospital and all hospitals together.

	1		2		3		4		5		6		all hospitals		p
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
# patients	400		317		328		451		260		402		2158		
Stage IV	321	80,3%	272	85,8%	269	82,0%	365	80,9%	214	82,3%	325	80,8%	1766	81,8%	0,47
Gender (male)	244	61,0%	186	58,7%	188	57,3%	278	61,6%	144	55,4%	253	62,9%	1293	59,9%	0,34
Age (mean (SD)) (years)	66,7 (11,2)		67,6 (10,6)		69,0 (11,3)		67,2 (10,6)		67,1 (10,8)		68,1 (11,2)		67,6 (11,0)		0,08
Follow up (median (IQR)) (days)	140 (49–362)		160 (62–359)		180 (63–366)		142 (56–349)		136 (45–354)		156 (43–363)		154 (51–359)		0,34
Year of diagnosis															0,33
2008	78	19,5%	44	13,9%	66	20,1%	76	16,9%	44	16,9%	72	17,9%	380	17,6%	
2009	85	21,3%	61	19,2%	62	18,9%	93	20,6%	35	13,5%	77	19,2%	413	19,1%	
2010	77	19,3%	81	25,6%	57	17,4%	92	20,4%	59	22,7%	74	18,4%	440	20,4%	
2011	78	19,5%	55	17,4%	70	21,3%	99	22,0%	68	26,2%	109	27,1%	479	22,2%	
2012	82	20,5%	76	24,0%	73	22,3%	91	20,2%	54	20,8%	70	17,4%	446	20,7%	
Performance status															0,00
0	146	38,6%	101	41,7%	102	32,8%	115	26,1%	99	43,0%	93	23,6%	656	32,9%	
1	135	35,7%	79	32,6%	107	34,4%	168	38,2%	62	27,0%	177	44,9%	728	36,5%	
2	45	11,9%	31	12,8%	52	16,7%	71	16,1%	28	12,2%	84	21,3%	311	15,6%	
3	52	13,8%	31	12,8%	50	16,1%	86	19,5%	41	17,8%	40	10,2%	300	15,0%	
Missing	22		75		17		11		30		8		163		
Squamous histology	65	16,3%	66	20,8%	65	19,8%	101	22,4%	49	18,8%	73	18,2%	419	19,4%	0,31

based on the drug prescription and dispensing data, we constructed early discontinuation of treatment (<4 cycles) and dose reductions (<80% of the initial dose) as additional patients' outcomes.

2.4. Statistical analysis

SPSS Statistics (version 24.0) was used for the statistical analysis. Age was categorized into three categories: under 65 years, 65–74, and 75 years or older. Tumour histology was categorized into squamous and non-squamous. Descriptive data were composed for the total sample, per year and per hospital stratified by various patient characteristics. From the individual treatment data several indicators were constructed including: percentage of patients treated with chemotherapy, percentage of different first line treatments options, and number and percentage of switches, dose reductions, and early discontinuation.

Between groups frequencies were compared using a chi square test, means using a one-way ANOVA test, and survival time between categories using a Log-Rank test. A p-value of <0.05 was considered significant. To identify patient characteristics that are associated with early discontinuation without any subsequent systemic treatment, univariate and multivariable logistic regression was planned. Patients receiving a second line treatment were excluded from the analysis.

3. Results

A total of 2619 NSCLC stage IIIB/IV patients could be selected from the CfO lung cancer database. From this selection, we excluded 13 patients because follow-up data was not available and 448 patients because the hospital of primary treatment was not the hospital of diagnosis resulting in a cohort of 2158 patients. The patient characteristics are described in Table 1. The majority of patients (81.8%) were diagnosed with stage IV NSCLC and the mean age was 68 years. More than 25% of patients had a PS of 2 or 3 at the time of diagnosis. No statistical differences were observed between hospitals for disease stage, gender, and age whereas PS did significantly differ between hospitals ($p < 0.05$).

Overall, 47,9% of all patients received any systemic treatment, 33,7% of those receiving first line treatment received second line treatment. Third line was started in 30,5% of those receiving second line treatment. A small but increasing number of patients was treated with maintenance treatment as part of their first line treatment (0,5% for year of diagnosis 2008, 5,8% in 2012) but no increase in the use of systemic treatment was observed over the years for any of the lines of treatment (supplemental Table 1). Fig. 1 depicts the percentage of patients treated with systemic treatment stratified by age category, gender, disease stage, PS and hospital of diagnosis and treatment. Treatment frequencies were statistically different between age categories, disease stage, PS and hospital (all $p < 0.001$). Patients not receiving systemic treatment received best supportive care (including palliative radiotherapy in 12,7% of those patients).

Variation in first line treatments was limited with seven regimens accounting for almost 90% of all first line treatments. Moreover more than 75% of all first line regimens were platinum based regimens with either gemcitabine or pemetrexed. The top-7 prescribed first line regimens and their frequencies (%) are presented in Fig. 2. A quarter of the other group was represented by TKI users.

Once first line treatment was started, approximately half of the patients received four or more cycles (Table 2). Of note, additional cycles after discontinuation of the initial treatment due to toxicity were considered cycles part of first line treatment (e.g. 1 cycle of cisplatin gemcitabine followed by 3 cycles of carboplatin gemcitabine results in a total of 4 cycles). Furthermore, dose reductions were found for 20% of all patients in any line of treatment (Table 2). A switch to other systemic agents due to toxicity was found in 15% of all first line treatment, mostly involving cisplatin based regimens. Significant interhospital differences were observed for the number of cycles administered (<4 cycles versus >=4 cycles) and the number of switches (Table 2).

Univariate logistic regression only revealed performance status to be associated with the outcome of early discontinuation in 686 patients receiving first line treatment only. Performance status 0–1 and 2–3 were grouped because odds ratios (OR) were similar (PS0, reference; PS1, 1.17; PS2, 2,19; PS3, 2,00). The OR for PS 2–3 versus PS 0–1 for early discontinuation was 1.97 (1,20–3,23, p = 0,007).

Median survival times in days for the total population, untreated and systemically treated population only are presented in Table 3. In the total population, the median survival was significantly higher for disease stage IIIB, women, younger patients

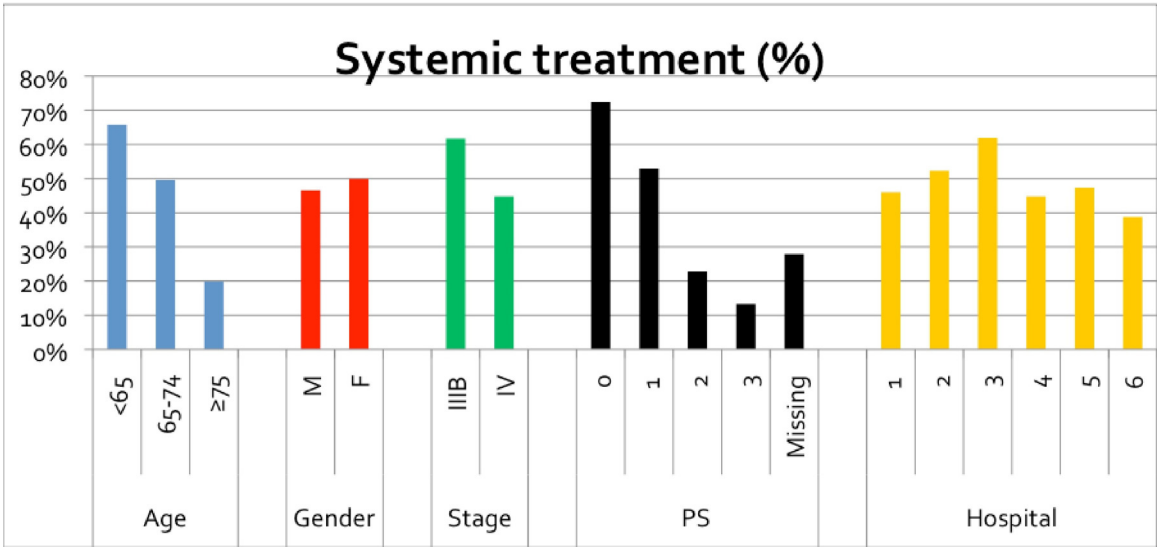

Fig. 1. Histogram. Percentage of patients systemically treated stratified by age, gender, disease stage, PS and hospital.

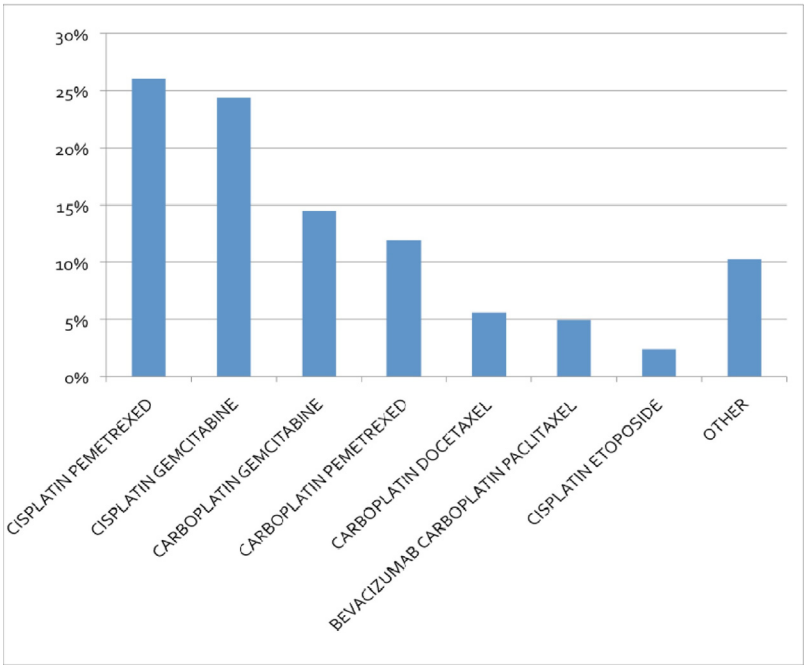

Fig. 2. Regimens started in the first line of treatment presented as percentage.

and better PS. There was no difference in median survival between hospitals and between years of diagnosis. Although the median survival did statistically differ between age categories for the total population and the treated population, the median survival was not lower for patients of 75 years of age and older when treated systemically.

4. Discussion

We have provided a detailed overview of daily practice in the systemic palliative treatment of NSCLC stage IIIB/IV in six Dutch teaching hospitals over a period of five years (2008–2012). Additionally, we investigated possible associations between patient characteristics and early discontinuation and we evaluated overall survival.

In this large cohort of NSCLC stage IIIB/IV 47,9% of patients received first line systemic treatment (44,8% stage IV, 61,7% stage IIIB). In line with our results, Brule et al. recently showed in their Canadian single centre study 55% of all advanced NSCLC patients received palliative systemic treatment in the same time window (2009–2012) [4]. Another study found 34% of all patients diagnosed with stage IV NSCLC and seen by an oncologist from 2005 to 2009 received systemic treatment [5]. Second line treatment was started for 51% [4] and 33% [5] of all patients treated with first line systemic treatment, whereas 34% of the patients in our study received second line treatment.

The median survival of patients that were treated systemically was 10,0 months, comparable to previously reported real world survival outcomes [4,5,12]. Consistently with other research, we found patients >75 years to have a median survival similar to those of younger patients [5]. Furthermore, the survival of systemically treated patients with a PS of 3 was 5,8 months whereas Salloum et al. showed in their observational (time window 2000–2007) study patients stage IIIB-IV with a poor PS (3 or 4) to have a median survival of 4,8 months [6]. Furthermore, we did not observe an increase in overall survival over the years. A large observational study from the United States also found no difference in overall survival for patients diagnosed 2011 as compared to 2007 reporting a median survival of respectively 9,2 and 9,3 months [12].

To our knowledge no other observational study has investigated the number of cycles and dose reductions as outcome parameters in routine care. We showed 49% of patients received less than four cycles of their first line treatments. Comparing our results to the number of cycles administered in clinical trials is challenging given that many trials report median number of cycles and give up to six

Table 2
Frequencies and percentages of dose reductions, cycles, and switches per hospital and for all hospitals.

	1		2		3		4		5		6		all hospitals		p value
Number of patients															
	184		166		203		202		123		156		1034		
Patients with dose reduction (1 or all drugs within any line)															
	37	20%	28	17%	48	24%	48	24%	28	23%	19	12%	208	20%	0,052
Number of cycles															
>=4	**92**	**50%**	**121**	**73%**	**111**	**55%**	**80**	**40%**	**48**	**39%**	**81**	**52%**	**533**	**52%**	<0,001
3	41	22%	14	8%	34	17%	44	22%	20	16%	27	17%	180	17%	
2	33	18%	16	10%	33	16%	50	25%	24	20%	22	14%	178	17%	
1	18	10%	15	9%	25	12%	28	14%	31	25%	26	17%	143	14%	
Number of switches	41	22%	37	22%	21	10%	27	13%	7	6%	23	15%	156	15%	<0,001

Table 3
Median survival times in days with interquartil range (IQR) for the total population, untreated and systemically treated population stratified by disease stage, year of diagnosis, gender, age category, PS, and hospital.

		NO TREATMENT			TREATMENT			ALL PATIENTS		p
		Median (IQR)	n	p	Median (IQR)	n	p	Median (IQR)	n	
All patients		59 (25–145)	1124		299 (171–556)	1034		154 (51–359)	2158	
Stage of disease	IIIB	102 (44–261)	150	<0,001	416 (247–796)	242	<0,001	293 (109–617)	392	<0,001
	IV	54 (23–136)	974		276 (157–501)	792		133 (46–311)	1766	
Year of diagnosis	2008	71 (33–155)	209	0,60	305 (154–581)	171	0,38	139 (57–346)	380	0,90
	2009	54 (22–136)	218		314 (171–621)	195		143 (46–389)	413	
	2010	58 (22–142)	216		296 (174–593)	224		161 (57–354)	440	
	2011	60 (27–133)	259		341 (192–570)	220		152 (50–366)	479	
	2012	54 (25–169)	222		271 (167–520)	224		169 (50–353)	446	
Gender	Male	55 (23–137)	691	0,08	285 (163–500)	602	0,01	142 (47–334)	1293	<0,001
	Female	65 (29–161)	433		328 (180–631)	432		172 (58–398)	865	
Age category	<65	65 (27–139)	294	0,44	314 (183–598)	565	0,15	217 (87–436)	859	<0,001
	65–74	50 (26–132)	358		276 (151–510)	352		140 (46–339)	710	
	75+	67 (24–159)	472		315 (171–544)	117		89 (32–248)	589	
PS	0	107 (49–218)	181	<0,001	350 (194–634)	475	<0,001	277 (123–537)	656	<0,001
	1	87 (42–220)	343		284 (170–546)	385		194 (80–394)	728	
	2	49 (26–106)	240		231 (112–336)	71		69 (32–179)	311	
	3	35 (16–72)	260		175 (124–472)	40		44 (18–108)	300	
	Missing	41 (12–93)	100		248 (173–382)	63		86 (23–248)	163	
Hospital	1	56 (23–154)	216	0,43	305 (165–530)	184	0,74	140 (49–362)	400	0,70
	2	65 (31–133)	151		276 (174–558)	166		160 (62–359)	317	
	3	50 (20–119)	125		277 (146–459)	203		180 (63–366)	328	
	4	65 (30–142)	249		304 (169–533)	202		142 (56–349)	451	
	5	52 (23–133)	137		295 (172–646)	123		136 (45–354)	260	
	6	58 (24–175)	246		357 (201–590)	156		156 (43–363)	402	

cycles [7–9] whereas in Dutch clinical practice this is mostly four. Nevertheless, our logistic regression analysis shows an association between early discontinuation and poor PS, a population generally underrepresented in randomized clinical trials. Groene et al. conducted a similar analysis in patients diagnosed with invasive epithelial cancer of the oesophagus or stomach [10]. In addition to a poor PS, they found age to be inversely associated with palliative treatment completion, concluding that this information should be considered when balancing treatment benefits, toxicity and patients quality of life.

Interhospital differences were found for several outcomes such as (a) the proportion of patients treated systemically and (b) the number of cycles and switches. These observations show that, although guidelines exist, translation to clinical practice can result in significant interhospital variation in outcomes presented in our study. This variation should be further investigated but could reflect differences of insight regarding the systemic treatment of elderly, patients with poor PS, and handling of toxicity. Our data can fuel interhospital discussion with the aim of streamlining NSCLC treatment towards best practice. In terms of survival, interhospital differences for the proportion of patients treated systemically did not translate into survival differences considering the group of patients as a whole (treated and untreated). This observation and the fact that systemic treatment is strongly associated with a survival benefit, could reflect interhospital patient selection for systemic treatment. Some doctors will treat only those patient that are surely fit for systemic treatment whereas others will also start treatment for patients who are more likely to suffer from the toxic effects of systemic treatment. The net survival result for both approaches may be the same, whereas other outcomes that relate to the quality of life may well differ. More research is needed to address this hypothesis.

Strengths of our study include (a) large cohort representing an unselected population from patients diagnosed with advanced lung cancer in the Netherlands, (b) highly detailed and validated data about applied pharmacotherapy (c) the availability of a large set of relevant patient/clinical characteristics with low numbers of missing data (d) and the possibility to analyse dose reductions, switches and number of cycles administered. A limitation of our study is the incompleteness of data about TKI use. Until the end of 2012, Dutch patients were allowed to collect these medications through community pharmacies, whereas they are dispensed by the hospital pharmacy since. We think, however, that this limitation does not affect our analyses regarding first line treatment as these drugs are only applied as second or later line of treatment in the study period.

In this study, we have presented a detailed overview of daily practice in the systemic palliative treatment of NSCLC stage IIIB/IV over the years 2008–2012. Such detailed data can serve as reference data for follow-up of the adoption of novel systemic treatment options for advanced lung cancer. Besides this, the constructed database provides a valuable non-trial context to study real world effectiveness of both existing systemic treatments and future treatments. Comparative effectiveness research using real world data can help answer questions that relate to the external validity of results from RCTs. [11]. Moreover, the rapid development of new medical treatments will give rise to many more clinical questions that need to be answered but are financially and practically impossible to answer with RCTs only. As for CfO, patient reported outcome measures (PROMs) are prospectively collected as part of the Santeon CfO program since 2014, allowing evaluation of drug effectiveness in NSCLC beyond the outcome overall survival in the near future.

Authorship contribution statement

The ICMJE recommends that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributions

Study concepts: B. Peters, C. Cramer-vd Welle, A Smit, F. Schramel, E vd Garde

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Quality control of data & algorithms: B. Peters, C. Cramer-vd Welle, A Smit, F. Schramel, E vd Garde

Data analysis and interpretation: B. Peters, C. Cramer-vd Welle, A Smit, F. Schramel, E vd Garde

Statistical analysis: B. Peters, E vd Garde

Manuscript preparation: B. Peters, E vd Garde

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Manuscript review: B. Peters, C. Cramer-vd Welle, A Smit, F. Schramel, E vd Garde

Funding

This is an investigator-initiated study that received financial support from Roche Netherlands BV.

Conflict of interest statement

This is an investigator-initiated study that received financial support from Roche Netherlands BV. No other conflict of interest is applicable for any of the authors.

Acknowledgements

The authors thank Dr. Wim van den Bosch for establishing the Care for Outcome registry. Dr. Hadewig Colen, Dr. Mirjam Crul, Dr. Maarten Deenen, Dr. Rene van Hulst, and Mr. Yuhan Kho are acknowledged for their efforts to complete and validate the hospital pharmacy data.

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.canep.2017.08.001.

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