Lung Cancer 130 (2019) 216–225

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Treatment and outcome of 432 patients with extensive-stage small cell lung cancer in first, second and third line – Results from the prospective German TLK cohort study

Claus-Christoph Steffens[a], Corinna Elender[b], Ulrich Hutzschenreuter[c], Stephanie Dille[d], Adrian Binninger[e], Lisa Spring[e], Martina Jänicke[e], Norbert Marschner[f,*], the TLK-Group (Tumour Registry Lung Cancer)

[a] SKH Studien GmbH, Hamburg, Germany
[b] Klinikum Dortmund, Klinik Nord Onkologie und Pneumologie, Dortmund, Germany
[c] Hämatologisch-Onkologische Gemeinschaftspraxis, Nordhorn, Germany
[d] Medical Department, iOMEDICO, Freiburg, Germany
[e] Clinical Epidemiology and Health Economics, iOMEDICO, Freiburg, Germany
[f] Praxis für interdisziplinäre Onkologie und Hämatologie, Freiburg, Germany

ARTICLE INFO

Keywords:
Small cell lung cancer
Cohort studies
Palliative care
Clinical outcome
Outpatient care

ABSTRACT

Objectives: Despite intensive research, the therapeutic options in extensive-stage small cell lung cancer (SCLC) are still limited. Data from routine clinical practice, so-called "real-world data", are centrally important to assess and improve the standard of care. We present prospectively documented data on systemic first-, second- and third-line treatment, number of treatment lines and outcome parameters of patients treated by medical oncologists in Germany.

Materials and methods: This is a descriptive analysis on 432 patients with extensive-stage SCLC enrolled at start of first-line therapy into the prospective German clinical cohort study TLK (Tumour Registry Lung Cancer). Patients were recruited by 87 sites between February 2010 and December 2013 and followed-up individually for 3 years.

Results: The majority of patients (93%) received a first-line platinum-based combination therapy. Carboplatin plus etoposide was documented more frequently than cisplatin plus etoposide (46 vs. 35%); patients receiving carboplatin were older (68 vs. 63 years) and more often presented with poorer performance status (17 vs. 11% ECOG ≥ 2). Both regimens yielded similar response and survival rates. Median first-line overall survival (OS) was 10.2 months (95% confidence interval [CI] 8.6–12.3) for carboplatin plus etoposide and 12.2 months (95% CI 10.1–14.7) for cisplatin plus etoposide. Most patients (77%) would have been eligible for participation in a clinical trial. 50% of the patients received a second and 22% a third line of treatment. Median second-line OS was 5.8 months (95% CI 4.8–7.5), median third-line OS 5.7 months (95% CI 3.8–7.0).

Conclusion: To our knowledge, this is the first study of prospectively documented patients with extensive-stage SCLC in routine clinical practice. We present treatment algorithms as well as outcome parameters for a large cohort in first-, second- and third-line treatment. The survival times and response rates reported in this routine setting correspond to the respective measures from large prospective trials.

1. Introduction

Lung cancer is one of the most common malignancies and the leading cause of cancer related deaths in Germany; 59.900 new diagnoses are expected in 2020 [1]. Small cell lung cancer (SCLC) is a poorly differentiated tumour with immunohistochemical expression of neuroendocrine markers accounting for approximately 15% of all lung cancer cases [2]. In contrast to the more common non-SCLC (NSCLC), the histologic subtype of 85% of all lung cancer cases, SCLC is characterised by rapid proliferation, early metastatic spread and initial high sensitivity to chemo- and radiotherapy. Virtually all patients have a history of smoking. The majority of patients with SCLC are diagnosed at

* Corresponding author at: Praxis für interdisziplinäre Onkologie und Hämatologie, Wirthstrasse 11c, 79110 Freiburg, Germany.
E-mail address: manuskript@onkologie-freiburg.de (N. Marschner).

https://doi.org/10.1016/j.lungcan.2019.02.026
Received 20 November 2018; Received in revised form 30 January 2019; Accepted 24 February 2019
0169-5002/ © 2019 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

advanced stages (extensive-stage) and median overall survival (OS) ranges between 8 and 12 months [3–5].

Clinical practice guidelines in the US and Europe recommend a platinum-based chemotherapy with etoposide for the first-line treatment of extensive-stage SCLC [6,7]. After an initial response, almost all patients relapse with chemotherapy-resistant disease and those who are eligible for second-line treatment mostly receive topotecan. Although numerous studies on new therapeutic targets have been conducted, no significant improvement in survival has been demonstrated and thus, no new substance has been approved in the past two decades (reviewed in Refs. [8–11]). In 2016, checkpoint inhibitors and targeted agents showed promising results in early trials (reviewed in Ref. [8]), kindling hope in their potential to expand the standard treatment strategies in the future.

However, patients with lung cancer often present with comorbidities, high age and low performance status. Inclusion criteria of clinical trials often exclude these patients, leaving many questions unanswered: What is the main treatment choice and how many patients receive a second or third line of treatment? Are the majority of patients eligible to receive standard platinum-based combination therapy? What are the outcome expectations overall and of patients receiving second- or third-line chemotherapy?

The prospective, clinical cohort study TLK (Tumour Registry Lung Cancer) set out to answer most of these questions. We have shown before that the patients with advanced NSCLC in routine care had markedly different clinical characteristics compared to patients enrolled in randomised clinical trials [12,13]. Furthermore we showed that there was no difference in outcome or health-related quality of life for patients receiving the platinum compounds cisplatin or carboplatin in first-line treatment of advanced NSCLC in routine care [14].

In this article, we present comprehensive “real world” data from the TLK on 432 patients with extensive-stage SCLC treated by office-based medical oncologists and clinics in Germany from 2010 until 2016. We present treatment algorithms as well as outcome parameters, e.g. progression-free survival (PFS), OS and response rates for the first, second and third line of treatment. We look at the proportion of patients who would have been deemed ineligible for participation in a clinical trial and relate the outcome results from our cohort to previously published data.

2. Materials and methods

2.1. Data source

The TLK was an open, longitudinal, multicentre, observational, prospective cohort study which started in 2010 and was closed in 2016. The TLK was reviewed by the responsible ethics committee and is registered as Tumour Registry Lung Cancer at ClinicalTrials.gov (NCT01192919). Written informed consent was obtained from all patients. Patients were enrolled from February 2010 until December 2013 from all over Germany, and followed for up to three years or until death, loss to follow-up or withdrawal of consent. The TLK has previously been described in detail [14].

2.2. Cohort definition

During the recruiting phase, 2509 patients with NSCLC, SCLC, and mixed histology had been recruited into the project. The present analysis focuses on 432 patients with metastatic or locally advanced, inoperable SCLC (extensive-stage), recruited from 87 sites, who received at least one palliative line of treatment. Second-line (third-line) chemotherapy was defined as the systemic treatment administered after discontinuing first-line (second-line) chemotherapy, either for intolerance or for progressive/recurrent disease as documented by the respective physician. Re-challenges with the same or similar chemotherapy were considered a subsequent line of treatment if documented as such by the respective physician. In order to avoid an overestimation of survival times due to retrospective data collection, we included only prospectively enrolled patients (n = 338) into the analysis of response, PFS and OS (all patients, who had signed informed consent no longer than 42 days after start of first-line treatment). Patient characteristics of the prospectively enrolled patients did not differ from those of the whole cohort. The tumour response was documented as best (clinical) response by the physician and not at previously specified time points according to RECIST criteria.

2.3. Statistical analysis

OS was defined as the interval between start of first-line (second- or third-line) treatment and the date of death from any cause. Patients alive or lost to follow-up at data cut (January 31, 2016) were censored at last contact according to the Kaplan-Meier method. To detect a potential overestimation of outcome data, patients recruited before and after start of first-line treatment were analysed in separate groups as well as all together. PFS was defined as the interval between start of first-line (second- or third-line) treatment and the date of progression or death. Patients without such an event before start of second-line (third-line or fourth-line) treatment were censored at either the start of second-line (third-line or fourth-line) treatment or at last contact. Kaplan-Meier estimates were calculated using SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2002–2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. All other analyses were performed using STATISTICA (StatSoft, Inc.) and IBM SPSS Statistics version 19.0.

3. Results

3.1. Patient, tumour and treatment characteristics

Table 1 presents the patient and tumour characteristics of the 432 patients with extensive-stage SCLC included into this analysis. Median age at start of therapy was 66 years and at least 86% of the patients were current or former smokers. 24% of the patients were in good general condition (ECOG = 0), 17% reported a poorer performance status (ECOG ≥ 2).

Patients receiving a combination therapy with cisplatin and etoposide in first-line treatment were younger at start of therapy (median age 63 years) and presented less frequently with a poor performance status (11% ECOG ≥ 2) than patients receiving carboplatin combinations (median age 68 years, 17% ECOG ≥ 2, Table 1). Generally, patients receiving platinum-combinations were younger and less often had a poor performance status (ECOG ≥ 2) than patients receiving platinum-free chemotherapy. A total of 174 patients (40%) received at least one cranial irradiation.

23% of our cohort (101 patients) could be considered as “trial-ineligible”, defined by the presence of at least one of the common exclusion criteria in clinical trials at start of first-line treatment: prior treatment, ECOG ≥ 2, severe kidney disease, moderate or severe liver disease, chronic heart failure, coronary heart disease, secondary or metastatic secondary tumours. 87 (86%) of these patients received standard platinum-based therapy.

Table 1
Patient and tumour characteristics – first-line.

Characteristic	Carboplatin + etoposide ± X[a] (n = 219)		Cisplatin + etoposide ± X[a] (n = 154)		Platinum-based[b] (n = 30)		Platinum-free[c] (n = 29)		All patients (n = 432)	
	Median	**Min-Max**	**Median**	**Min-Max**	**Median**	**Min-Max**	**Median**	**Min-Max**	**Median**	**Min-Max**
Age at start of therapy, years	67.6	39-88	63.0	34-89	62.1	45-81	70.0	45-84	65.7	34-89
	Mean	**StD**	**Mean**	**StD**	**Mean**	**StD**	**Mean**	**StD**	**Mean**	**StD**
BMI at start of therapy, kg/m^2	26.4	5.0	25.9	5.1	27.8	12.6	24.9	4.7	26.2	5.9
Sex	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Female	77	35.2	62	40.3	16	53.3	11	37.9	166	38.4
Male	141	64.4	92	59.7	14	46.7	18	62.1	265	61.3
Patients with comorbidity[d]										
Any comorbidity[e]	171	78.1	103	75.9	26	86.7	22	75.9	322	74.5
CCI = 0[f]	134	61.2	98	63.6	16	53.3	15	51.7	263	60.9
CCI ≥1[f]	85	38.8	56	36.4	14	46.7	14	48.3	169	39.1
Chronic lung disease	48	21.9	34	22.1	9	30.0	4	13.8	95	22.0
Diabetes mellitus	34	16.0	24	15.6	5	16.7	5	17.2	69	16.0
Hypertension	102	46.6	44	28.6	13	43.3	11	37.9	170	39.4
Haemoglobin < 10 g/dL										
Yes	21	9.6	12	7.8	5	16.7	9	31.0	47	10.9
No	191	87.2	140	90.9	25	83.3	19	65.5	375	86.8
Unknown	7	3.2	2	1.3	0	0.0	1	3.4	10	2.4
LDH > upper norm										
Yes	105	47.9	63	40.9	13	43.3	16	55.2	197	45.6
No	85	38.8	79	51.3	13	43.3	11	37.9	188	43.5
Unknown	29	13.2	12	7.8	4	13.3	2	6.9	47	10.9
Calcium > upper norm										
Yes	10	4.6	2	1.3	1	3.3	2	6.9	15	3.5
No	180	82.2	133	86.4	26	86.7	26	89.7	365	84.5
unknown	29	13.2	19	12.3	3	10.0	1	3.4	52	12.0
Performance status[d]										
ECOG = 0	48	21.9	38	24.7	9	30.0	8	27.6	103	23.8
ECOG =1	117	53.4	79	51.3	13	43.3	9	31.0	218	50.5
ECOG ≥ 2	38	17.4	17	11.0	6	20.0	11	37.9	72	16.7
Missing	16	7.3	20	13.0	2	6.7	1	3.4	39	9.0
Metastasis at start of 1st-line[g]										
Yes	164	74.9	106	68.8	19	63.3	19	65.5	308	71.3
No	2	0.9	4	2.6	0	0	0	0	6	1.4
Missing	53	24.2	44	28.6	11	36.7	10	34.5	118	27.3
Trial eligibility[h]										
Potentially trial-eligible	167	76.3	125	81.2	24	80.0	15	51.7	331	76.6
Trial-ineligible	52	23.7	29	18.8	6	20.0	14	48.3	101	23.4
Smoking status[d]										
Current Smoker	58	26.5	50	32.5	13	43.3	9	31.0	130	30.1
History of smoking[i]	129	58.9	85	55.2	12	40.0	14	48.3	240	55.6
Never Smoker	12	5.5	3	1.9	1	3.3	2	6.9	18	4.2
Unknown	20	9.1	16	10.4	4	13.3	4	13.8	44	10.2

Abbreviations: BMI, body mass index; LDH, lactate dehydrogenase; Max, maximum; Min, minimum; StD, standard deviation; X, any substance other than carboplatin, cisplatin or etoposide.

[a] A third substance "X" (mostly vincristine) was given to 8.7% of the patients receiving carboplatin + etoposide and 1.3% of the patients receiving cisplatin + etoposide.

[b] Platinum-based: any regimen with cisplatin or carboplatin but without etoposide.

[c] Platinum-free: any regimen without platinum-agent.

[d] At enrolment.

[e] At least one comorbidity according to Charlson or additional concomitant diseases.

[f] Charlson Comorbidity Index (CCI) according to Quan et al. [28,29].

[g] 8 weeks before until 4 weeks after start of first-line treatment.

[h] Trial-eligibility was defined by the presence of at least one of the following exclusion criteria: prior treatment, ECOG ≥ 2, severe kidney disease, moderate or severe liver disease, chronic heart failure, coronary heart disease, metastatic secondary tumours.

[i] former or ever smoker.

3.2. Choice of systemic treatment

First-line treatments were started between May 2009 until November 2013. In total, 93% of the patients received a platinum-based combination chemotherapy. The four main treatment strategies are shown in Fig. 1A. 86% of the patients received a platinum agent combined with etoposide in their first line of treatment; 10% of the patients additionally received a third substance (mostly vincristine). Looking at the most frequently prescribed regimens, 46% of the patients received carboplatin with etoposide and 35% cisplatin with etoposide

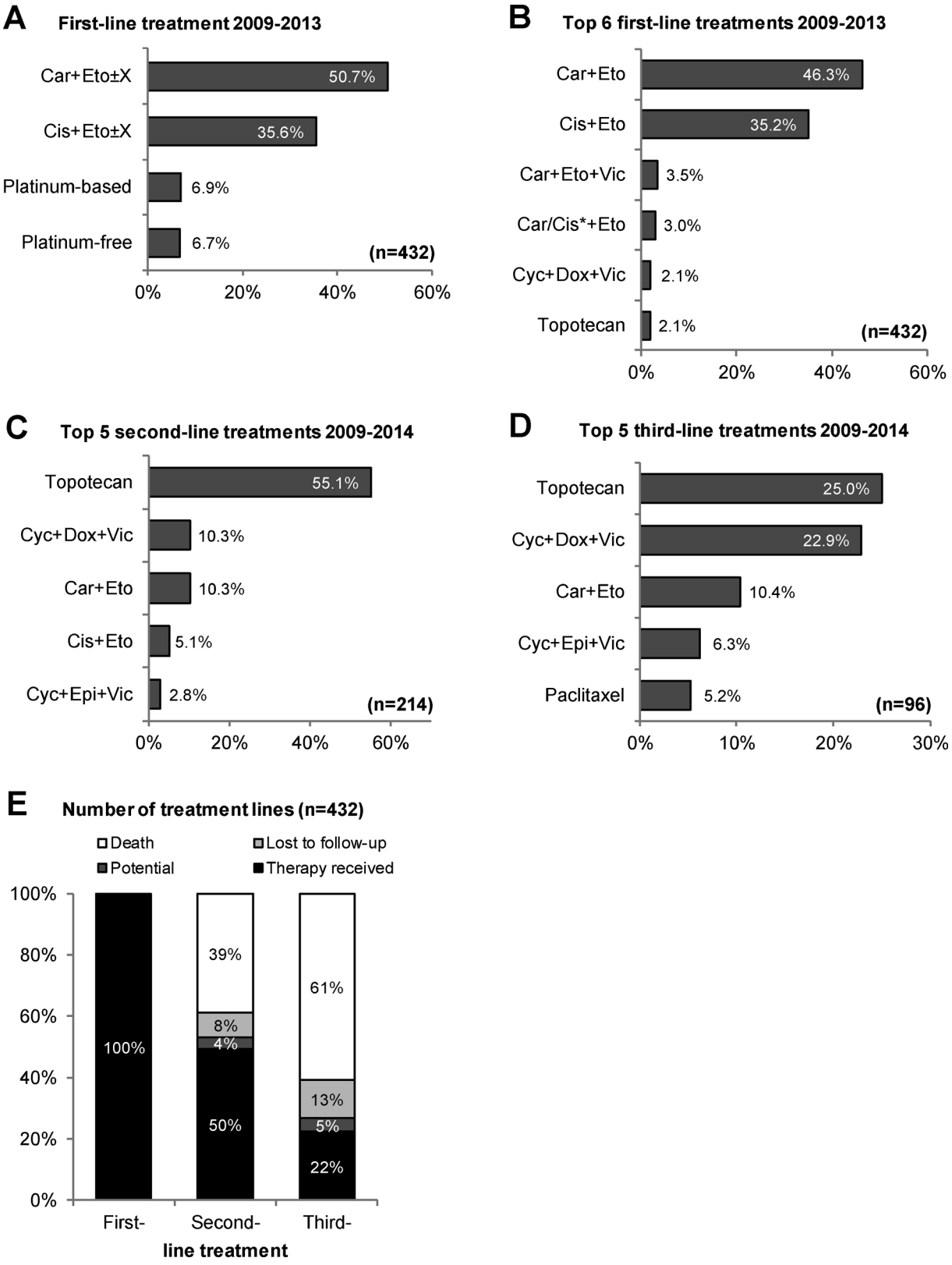

Fig. 1. Choice of systemic treatment in advanced SCLC.
(A) Distribution of first-line treatments from 2009-2013. A third substance "X" was given to 8.7% of the patients receiving carboplatin + etoposide and 1.3% of the patients receiving cisplatin + etoposide. **(B)** Top 5 first-line treatments sorted by frequency (n = 432) from 2009-2013. *Car/Cis: patients switched from carboplatin to cisplatin or vice versa within first-line treatment. **(C)** Top 5 second-line treatments sorted by frequency (n = 214) from 2009-2014. **(D)** Top 5 third-line treatments sorted by frequency (n = 96) from 2009-2014. **(E)** Percentage of patients receiving a palliative second- or third-line treatment (n = 432). Potential: further treatment possible (current line ongoing, therapy paused or documentation finished).
Abbreviations: Car, carboplatin; Cis, cisplatin; Cyc, cyclophosphamide, Dox, doxorubicin; Epi, epirubicin; Eto, etoposide; platinum-based, any regimen with cisplatin or carboplatin but without etoposide; platinum-free, any regimen without platinum agent; Vic, vincristine; X, any other substance than carboplatin, cisplatin or etoposide.

Table 2
OS, PFS and best response of prospectively documented patients – first-line.

	Carboplatin + etoposide ± X (n = 173)		Cisplatin + etoposide ± X (n = 119)		Platinum-based (n = 22)		Platinum-free (n = 24)		All patients (n = 338)	
Best response	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**
CR/PR	103	59.5	69	58.0	11	50.0	10	41.7	193	57.1
SD	26	15.0	18	15.1	0	0.0	0	0.0	44	13.0
PD	15	8.7	12	10.1	5	22.7	5	20.8	37	10.9
Not evaluable	29	16.8	20	16.8	6	27.3	9	37.5	64	18.9
Number of cycles	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
	6.0	2.0	6.0	3.0	4.0	3.25	3.5	3.75	5.0	3.0
PFS	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Events	140	80.9	80	67.2	18	81.8	21	87.5	259	76.6
Median	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**
	6.9	6.2-7.4	7.9	6.5-8.8	5.2	3.1-6.7	2.2	1.5-5.0	6.8	6.2-7.4
Survival rate	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
6 months	60.2	52.3-67.1	64.9	54.9-73.2	38.4	18.5-58.1	29.2	13.0-47.6	58.1	52.4-63.3
12 months	19.2	13.2-26.0	25.3	16.8-34.6	11.0	1.0-34.6	12.5	3.1-28.7	20.3	15.7-25.3
OS	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Events	141	81.5	88	73.9	18	81.1	20	83.3	267	79.0
Median	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**
	10.2	8.6-12.3	12.2	10.1-14.7	9.3	5.1-14.5	6.5	1.7-10.7	10.7	9.3-11.8
Survival rate	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
6 months	75.1	67.8-80.9	85.9	78.1-91.2	63.6	40.3-79.9	50	29.1-67.8	76.2	71.2-80.5
12 months	43.2	35.3-50.8	53.0	43.1-61.9	32.0	13.5-52.4	18.2	5.8-36.1	44.0	38.4-49.5

Abbreviations: CI, confidence interval; CR, complete response; IQR, interquartile range; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; StD, standard deviation; X, any substance other than carboplatin, cisplatin or etoposide.

(Fig. 1B). 3% of the patients switched from carboplatin to cisplatin or vice versa within first-line treatment (Fig. 1B).

In second-line, most patients received topotecan monotherapy (55%) or other platinum-free regimens (Fig. 1C). The top three second-line regimens accounted for 76% of treatments. 47 patients (22% of all patients receiving second-line treatment) were re-challenged with a platinum agent. In third-line, the choice of treatments broadened: 25% of the patients received topotecan and 23% a combination of cyclophosphamide, doxorubicin and vincristine. A total of 18 patients (19% of all patients receiving third-line treatment) were re-challenged with a platinum agent in third line of treatment, 10% with carboplatin and etoposide (Fig. 1D). Of all patients, who received a third line of treatment, 61 (64%) received 3 distinct lines of treatment. Patients receiving a third line of treatment were slightly younger (63.7 years vs. 65.7 years), more often female (46% vs. 38%) and in good overall condition (ECOG = 0 35% vs. 24% at start of first-line) than the overall cohort of patients starting first-line treatment.

In total, at least 50% of the patients (n = 214) received a second line of treatment and at least 22% of the patients received a third line (Fig. 1E). 39% of the patients died prior to a second-line and 61% prior to a third-line treatment. Patients marked as “potential” were alive at database closure and could potentially have received further treatment (had either not completed the previous line of treatment or had finished the previous line but not started a new one yet). In total, 13% of the patients (n = 54) were lost to follow-up.

3.3. Outcome parameters for first-line treatment

For all prospectively documented patients (n = 338), response rates and outcome data according to the different treatment regimens are shown in Table 2. Looking at the therapy cycles, patients received a median of 3.5 (platinum-free) or 6.0 (Car + Eto ± X and Cis + Eto ± X) cycles (Table 2). Chemotherapy was successful in 70% of all patients, as assessed by the disease control rate, covering complete or partial response (CR/PR) and stable disease (SD). Similar disease control rates were observed for patients receiving platinum-etoposide combinations, while the disease control rate was markedly lower in patients receiving other platinum-based regimens (50%) or platinum-free regimens (42%).

Median first-line PFS was 6.9 months and median OS 10.2 months for combinations with carboplatin-etoposide. Median first-line PFS was 7.9 months and median OS 12.2 months for combinations with cisplatin-etoposide. Median first-line PFS of all prospectively documented patients was 6.8 months (Table 2, Fig. 2A) and median OS was 10.7 months (Table 2, Fig. 2B). First-line PFS and OS by treatment strategy are shown in Supplemental Figure S1. Of note, patients receiving these regimens differed in important sociodemographic and medical parameters (see Section 3.1 and Table 1). The survival times of potentially trial-eligible and trial-ineligible patients did not differ significantly: median PFS was 7.1 months (95% CI 6.4–7.8) and median OS 12.1 months (95% CI 10.9–13.3) for potentially trial-eligible patients (n = 257), median PFS was 6.4 months (95% CI 5.1–7.7), median OS 8.9 months (95% CI 6.9–10.9) for trial-ineligible patients (n = 81).

3.4. Outcome parameters for second- and third-line treatment

Taking a closer look at all prospectively documented patients who had received a second line of treatment (n = 155), median age at start

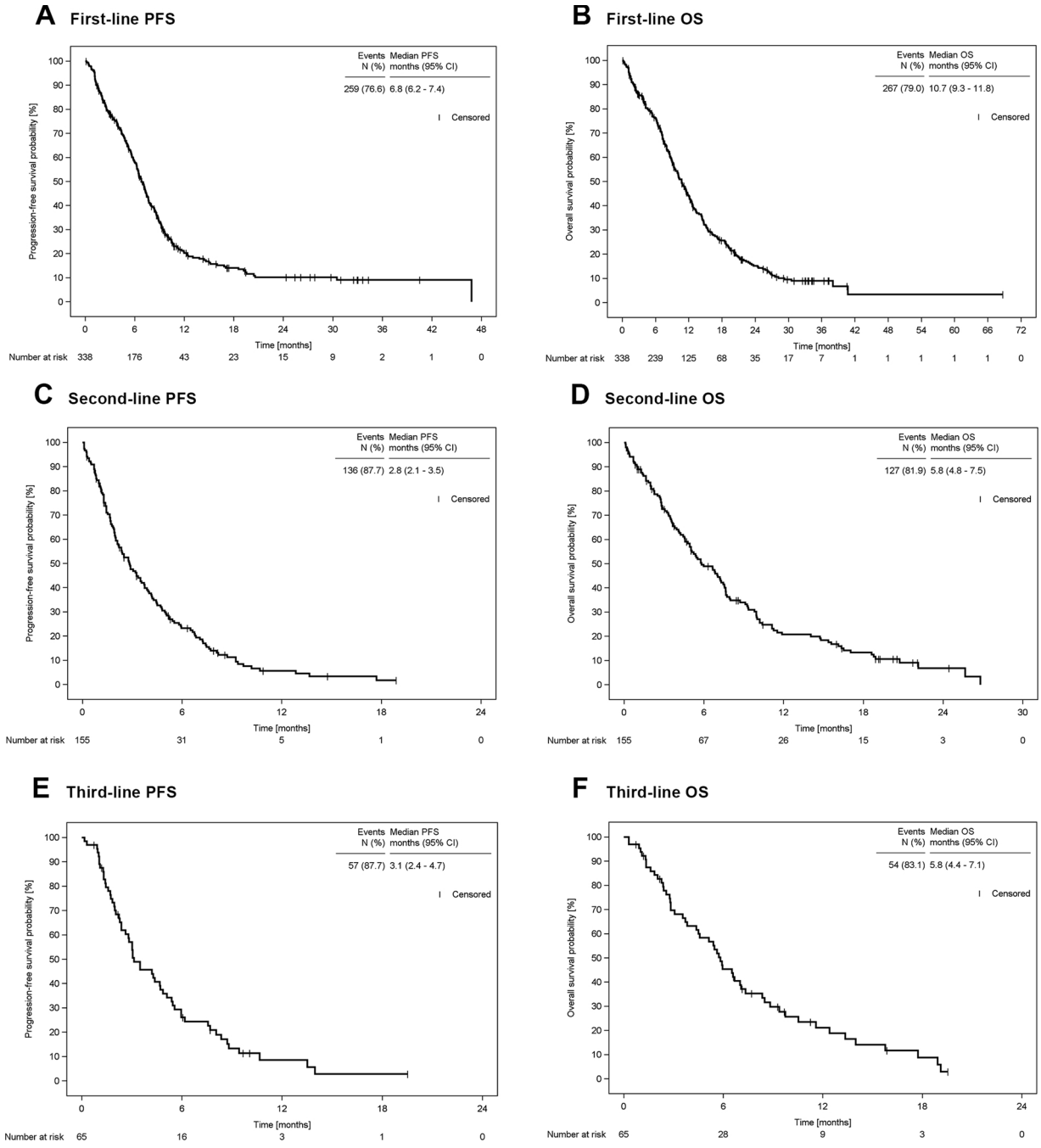

Fig. 2. Progression-free and overall survival.
(A) First-line PFS and **(B)** first-line OS of all prospectively enrolled patients (n = 338), **(C)** Second-line PFS and **(D)** second-line OS, **(E)** third-line PFS and **(F)** third-line OS.
Abbreviations: CI, confidence interval; OS, overall survival; | Censored.

of second-line treatment was 64 years (Table 3). 22% of the patients achieved a complete or partial response. Patients receiving topotecan monotherapy in second-line were older (median age 66 years) than patients receiving other treatment options (median age 61 years). Median second-line PFS was 2.8 months (95% CI 2.1–3.5, Figure S1A), and median second-line OS was 5.8 months (95% CI 4.8–7.5, Fig. 2C and D).

Also, in third-line treatment (65 prospectively documented patients), median age at start of treatment was 64 years (Table 4), with patients receiving topotecan monotherapy being older (median age 70 years) than patients receiving other treatments (median age 63 years). Median third-line PFS was 3.1 months (95% CI 2.4–4.7) and median third-line OS was 5.8 months (95% CI 4.4–7.1, Fig. 2E and F).

18 patients (4%) subsequently received a fourth and 8 patients (2%) a fifth line of treatment.

Table 3
Patient characteristics and outcome parameter of all prospectively documented patients receiving a second-line treatment.

	Topotecan[a] (n = 94)		Platinum-based[b,d] (n = 31)		Platinum-free[c] (n = 30)		All patients (n = 155)	
	Median	**Min-Max**	**Median**	**Min-Max**	**Median**	**Min-Max**	**Median**	**Min-Max**
Age, years	66.4	46-84	61.3	45-79	61.5	39-78	64.4	39-84
Sex	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Female	31	33.0	16	51.6	11	36.7	58	37.4
Male	63	67.0	15	48.4	19	63.3	97	62.6
First-line treatment [months]	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Duration[e]	3.5	0.85	2.4	2.4	3.5	1.7	3.5	1.4
Time to next treatment[f]	8.0	4.27	6.6	8.3	6.2	5.9	7.8	5.3
Treatment-free interval[g]	4.2	4.3	4.2	6.57	2.3	4.0	4.0	5.0
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
< 3 months	26	27.7	14	45.2	19	63.4	59	38.1
3-6 months	40	42.6	6	19.4	7	23.3	53	34.2
> 6 months	28	29.8	11	35.5	4	13.3	43	27.7
Best response	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
CR/PR	13	13.8	12	38.7	9	30.0	34	21.9
SD	13	13.8	3	9.7	4	13.3	20	12.9
PD	38	40.4	8	25.8	5	16.7	51	32.9
Not evaluable[h]	30	31.9	8	25.8	12	40.0	50	32.3
Number of cycles	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
	3.0	3.0	3.0	3.0	4.0	4.0	3.0	3.5
PFS	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Events	88	93.6	20	64.5	28	93.3	136	87.7
Median	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**
	2.3	1.8 - 2.9	4.5	2.9 - 10.2	3.4	1.4 - 5.1	2.8	2.1-3.5
OS	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Events	80	85.1	22	71.0	25	83.3	127	81.9
Median	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**
	5.2	3.8-7.2	8.0	6.8-16.5	5.0	3.5-9.1	5.8	4.8-7.5

Abbreviations: CI, confidence interval; CR, complete response; IQR, interquartile range; Max, maximum; Min, minimum; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; StD, standard deviation; X, any substance other than carboplatin, cisplatin or etoposide.

[a] Topotecan monotherapy.

[b] Platinum-based: any regimen with cisplatin or carboplatin (1 patient received carboplatin and topotecan).

[c] Platinum-free: any regimen without platinum-agent or topotecan.

[d] Second-line chemotherapy was defined as the systemic treatment administered after discontinuing first-line chemotherapy, either for intolerance or for progressive/recurrent disease.

[e] Time period between start of first-line treatment until end of first-line treatment.

[f] Time period between start of first-line treatment until start of second-line treatment.

[g] Time period between end of first-line treatment until start of second-line treatment.

[h] Due to the high number of ongoing treatments and assessment of response as per local site standard (non-interventional design without independent review), a high percentage of responses is not evaluable.

Table 4
Patient characteristics and outcome parameter of all prospectively documented patients receiving a third-line treatment.

	Topotecan[a] (n = 15)		Platinum-based[b,d] (n = 12)		Platinum-free[c] (n = 38)		All patients (n = 65)	
	Median	**Min-Max**	**Median**	**Min-Max**	**Median**	**Min-Max**	**Median**	**Min-Max**
Age, years	69.8	48.2-78.8	62.9	45.0-83.7	63.0	46.0-82.1	63.7	45.0-83.7
Sex	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Female	7	53.3	3	25.0	20	52.6	30	46.2
Male	8	46.7	9	75.0	18	47.4	35	53.8
Best response	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
PR	1	6.7	2	16.7	2	5.3	5	7.7
SD	3	20.0	4	33.3	14	36.8	21	32.3
PD	4	26.7	1	8.3	12	31.6	17	26.2
Not evaluable [e]	7	46.7	5	41.7	10	26.3	22	33.8
PFS	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Events	12	80.0	10	83.3	35	92.1	57	87.7
Median	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**
	1.8	1.1-5.4	5.6	2.0-10.6	3.5	2.8-4.7	3.1	2.4-4.7
OS	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Events	12	80.0	9	75	33	86.8	54	83.1
Median	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**	**Months**	**95% CI**
	2.8	1.1-7.1	7.0	2.3-15.8	5.7	4.4-8.4	5.8	4.4-7.1

Abbreviations: CI, confidence interval; CR, complete response; Max, maximum; Min, minimum; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a] Topotecan monotherapy.

[b] Platinum-based: any regimen with cisplatin or carboplatin (1 patient received cisplatin and topotecan).

[c] Platinum-free: any regimen without platinum-agent or topotecan.

[d] Third-line chemotherapy was defined as the systemic treatment administered after discontinuing second-line chemotherapy, either for intolerance or for progressive/recurrent disease.

[e] Due to the high number of ongoing treatments and assessment of response as per local site standard (non-interventional design without independent review), a high percentage of responses is not evaluable.

4. Discussion

This study is the first of its kind evaluating data from a large prospectively documented cohort of patients with extensive-stage SCLC in German routine clinical practice. At least 50% of the patients received a second- and 22% a third line of treatment. Platinum-based combination chemotherapies accounted for 93% of all first-line treatments between 2009 and 2013. The two main treatment regimens were carboplatin or cisplatin combined with etoposide (51% and 36%, respectively). Patients receiving carboplatin-based combination therapy were older and presented more frequently with a poorer performance status than patients receiving cisplatin-based combinations. However, both regimens yielded similar response rates, PFS and OS. The survival times and response rates reported in our routine setting correspond to the respective measures from large prospective trials, even though this cohort comprised 101 patients (23%) who would have been ineligible for participation in a clinical trial according to common exclusion criteria.

This study was designed to examine the treatment and outcome of patients receiving systemic therapy. Therefore, results may not be generalised to the small group of patients not receiving any systemic treatment. The non-interventional design of this study (no randomisation) precludes causal conclusions on differences of effectiveness of the different treatment strategies. In the TLK registry, there were no specifications as to the timing, frequency or criteria of tumour assessment and thus PFS data should be considered as the best clinical approximation and might not be identical to the PFS determined in clinical trials. A distinct proportion of patients was re-challenged with a similar regimen (22% of the patients in second- and 19% of the patients in third-line treatment) and thus not all patients in third-line treatment received three distinct chemotherapeutic agents. Strengths of this project are the prospective data collection and the participation of oncologists all over Germany recruiting a large study cohort.

After more than 40 failed phase III trials in the past four decades, the list of ineffective drugs for SCLC is long [13,14]. For those patients with a good performance status, a combination of cisplatin and etoposide is considered the gold standard [14]. In clinical practice, however, carboplatin is frequently used instead of cisplatin, especially in older patients [15–17]. Also in our cohort, combinations based on etoposide plus carboplatin were used more frequently than combinations based on etoposide plus cisplatin (51 vs. 36%) and patients receiving carboplatin were older (median age 68 vs. 63 years). Several studies have suggested that combination regimen with either cisplatin or carboplatin are comparable regarding ORR, PFS, and OS in first-line therapy: A meta-analysis of four randomised trials concluded that both regimens were equally effective (median OS 9.6 months for cisplatin and 9.4 months for carboplatin, with an overall response rate of 67% and 66%, respectively) and differed only in their toxicity profiles [15]. Similarly, studies at population-level found no significant difference in survival between combinations based on carboplatin or cisplatin [17,18]. Karam and colleagues reported a median OS of 11 months for carboplatin plus etoposide and 10 months for cisplatin plus etoposide for patients with extensive-stage SCLC in British Columbia from 2004 to 2008 [17]. These survival times are comparable with the times observed in our cohort, the median OS for carboplatin plus etoposide was 10.2 months and 12.2 months for cisplatin plus etoposide, the response rate was 60% and 58%, respectively. Thus, the choice of platinum agent in first-line therapy should primarily depend on expected toxicity, performance status and comorbidities [19]. Interestingly, a recent large randomised phase III trial specifically designed for extensive-stage SCLC showed that the combination regimen cisplatin plus etoposide failed to improve survival in comparison to an etoposide-containing regimen without cisplatin [20], providing a valid alternative to platinum-based therapy.

A recent review numbered the median survival of patients with extensive-stage SCLC between 7 and 10 months with a 1-year survival rate of 20% to 40% [14]. The outcome of the patients with extensive-stage SCLC in the TLK registry is at the upper end with a median OS of 10.7 months and a 1-year survival rate of 44%. In contrast to other

malignancies such as renal cell carcinoma [21], most patients with SCLC in routine care would be eligible for participation in a clinical trial (77%), suggesting that the results from these trials are conferrable to the majority of patients. Interestingly, 86% of the potentially trial-ineligible patients received standard platinum-based chemotherapy anyway.

A special characteristic of SCLC is its responsiveness to initial treatment, but most patients relapse with relatively resistant disease and a median survival of 4–5 months [16]. Correspondingly, the median second-line survival was 5.8 months in our cohort. The top three regimens accounted for 76% of treatments, reflecting the lack of individual alternatives. Indeed, topotecan is the only second-line drug approved by the FDA (US Food and Drug Administration), but so far, it has produced only modest anti-tumour effects with response rates of 5–24% and a median survival of roughly 6 months [9,22,23]. Also in our cohort, the median OS for patients receiving second-line topotecan was 5.2 months with a response rate of 14%. Due to the non-interventional design of this study, no causal conclusions can be drawn regarding the seemingly different survival times between the subgroups. More in-depth analysis with appropriate methods would require a higher number of patients or a specifically designed randomized clinical trial.

There is no consensus on the treatment of SCLC in the third-line setting, and only few patients actually go on to receive a third line of therapy: a multicentre, retrospective review documented 120 patients with third-line treatment over a period of 10 years; in their largest contributing centre, only 6% of all SCLC patients went on to receive 3 lines of chemotherapy [24]. A single-institution retrospective analysis reported 18% of the patients receiving third-line chemotherapy [25]. In our prospectively documented cohort, 22% of the patients received a third line of treatment. The previously reported survival times are in line with our results (median third-line PFS 3.1 months, OS 5.8 months): Simos et al reported a PFS of 2.0 months and an OS of 4.7 months [24], De Jong et al reported an OS of 5 months [25]. There are no guidelines on the choice of third-line treatment, as reflected in the wide variety of regimens reported. Additionally, many patients are re-challenged with a platinum-agent, in the report by Simos et al, only 20% of the patients received 3 distinct lines of chemotherapy [24]; compared to 64% of all patients receiving third-line treatment in our cohort, underlining the urgent need for novel therapeutic options.

Just recently, encouraging results have been published with the antibody-drug conjugate rovalpituzumab tesirine [23] as well as with the checkpoint inhibitors ipilimumab and/or nivolumab [26], with promising response rates in patients with recurrent SCLC [8]. Furthermore, the combination of first-line chemotherapy with the checkpoint inhibitor atezolizumab showed promising survival data [27]. It will be interesting to see the implementation of these new regimens in routine clinical practice and they will hopefully start the urgently needed improvement in survival and quality of life. The successor cohort study CRISP recruiting patients with lung cancer in Germany was started in December 2015 (ClinicalTrials.gov NCT02622581) and will continue to provide valuable insight into routine care of these patients.

5. Conclusion

This prospective cohort study shows that the majority of patients with extensive-stage SCLC in routine clinical practice (93%) received standard platinum-based combination therapy in their first line of treatment. Both combination therapies of carboplatin or cisplatin plus etoposide yielded similar response rates and survival times despite differences in patient characteristics. 50% of the patients went on to receive a second- and 22% a third-line treatment, mostly topotecan (55% in second- and 25% in third-line), with a median OS of approximately 6 months in both treatment lines. With 1 in 5 patients receiving a third line of treatment, guidelines as to the optimal choice of third-line treatment are urgently needed.

Acknowledgements

The authors thank all patients, physicians and study teams participating in the TLK. We thank Dr. Nicole Weger-Wölfing (iOMEDICO) for support during design and set-up of the project and Dr. Leonora Houet (iOMEDICO) for critical comments on the manuscript.

The TLK is designed, managed and analysed by iOMEDICO and has received continuous financial support from Boehringer Ingelheim Pharma GmbH & Co. KG, Onkovis GmbH, Roche Pharma AG and TEVA Deutschland GmbH. None of the funders had any role in study design, data collection and analysis, interpretation of results, decision to publish, or preparation of the manuscript.

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.2019.02.026.

References

[1] Z. für, K. im (Eds.), Bericht zum Krebsgeschehen in Deutschland 2016, R.K.-I. Robert-Koch-Institut, Berlin, 2016.
[2] R. Govindan, N. Page, D. Morgensztern, W. Read, R. Tierney, A. Vlahiotis, E.L. Spitznagel, J. Piccirillo, Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database, JCO 24 (2006) 4539–4544, https://doi.org/10.1200/JCO.2005.04.4859.
[3] M. Tiseo, L. Boni, F. Ambrosio, A. Camerini, E. Baldini, S. Cinieri, M. Brighenti, F. Zanelli, E. Defraia, R. Chiari, C. Dazzi, C. Tibaldi, G.M. Turolla, V. D'Alessandro, N. Zilembo, A.R. Trolese, F. Grossi, F. Riccardi, A. Ardizzoni, Italian, multicenter, phase III, randomized study of cisplatin plus etoposide with or without bevacizumab as first-line treatment in extensive-disease small-cell lung cancer: the GOIRC-AIFA FARM6PMFJM trial, J. Clin. Oncol. 35 (2017) 1281–1287, https://doi.org/10.1200/JCO.2016.69.4844.
[4] Y. Sun, Y. Cheng, X. Hao, J. Wang, C. Hu, B. Han, X. Liu, L. Zhang, H. Wan, Z. Xia, Y. Liu, W. Li, M. Hou, H. Zhang, Q. Xiu, Y. Zhu, J. Feng, S. Qin, X. Luo, Randomized phase III trial of amrubicin/cisplatin versus etoposide/cisplatin as first-line treatment for extensive small-cell lung cancer, BMC Cancer 16 (2016), https://doi.org/10.1186/s12885-016-2301-6.
[5] M. Fiegl, A. Pircher, C. Waldthaler, G. Gamerith, F. Kocher, G. Pall, M. Nevinny, T. Schmid, W. Sterlacci, H. Jamnig, G. Zangerl, A. Zabernigg, W. Oberaigner, W. Hilbe, Small steps of improvement in small-cell lung cancer (SCLC) within two decades: a comprehensive analysis of 484 patients, Lung Cancer 84 (2014) 168–174, https://doi.org/10.1016/j.lungcan.2014.02.005.
[6] M. Früh, D. De Ruysscher, S. Popat, L. Crinò, S. Peters, E. Felip, Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 24 (2013) vi99–vi105, https://doi.org/10.1093/annonc/mdt178.
[7] C.M. Rudin, N. Ismaila, C.L. Hann, N. Malhotra, B. Movsas, K. Norris, M.C. Pietanza, S.S. Ramalingam, A.T. Turrisi, G. Giaccone, Treatment of small-cell lung cancer: American Society Of Clinical Oncology Endorsement of the American College Of Chest Physicians Guideline, J. Clin. Oncol. 33 (2015) 4106–4111, https://doi.org/10.1200/JCO.2015.63.7918.
[8] A. Seeber, C. Leitner, K. Philipp-Abbrederis, G. Spizzo, F. Kocher, What's new in small cell lung cancer – extensive disease? An overview on advances of systemic treatment in 2016, Future Oncol. 13 (2017) 1427–1435, https://doi.org/10.2217/fon-2017-0046.
[9] L.A. Byers, C.M. Rudin, Small cell lung cancer: where do we go from here? Cancer 121 (2015) 664–672, https://doi.org/10.1002/cncr.29098.
[10] K. Kahnert, D. Kauffmann-Guerrero, R.M. Huber, SCLC–state of the art and what does the future have in store? Clin. Lung Cancer 17 (2016) 325–333, https://doi.org/10.1016/j.cllc.2016.05.014.
[11] F. Koinis, A. Kotsakis, V. Georgoulias, Small cell lung cancer (SCLC): no treatment advances in recent years, Transl. Lung Cancer Res. 5 (2016) 39–50, https://doi.org/10.3978/j.issn.2218-6751.2016.01.03.
[12] N. Marschner, M. Bertram, S. Kopfmann, U. von von Verschuer, H.W. Tessen, Overall survival and sequential treatment of patients with advanced NSCLC in German outpatients centres - data from the clinical TLK Registry, Onkologie 36 (suppl. 7) (2013) 29.
[13] H.W. Tessen, U. Hutzschenreuter, C.C. Steffens, A. Nusch, J. Spirik, N. Marschner, The treatment of lung cancer in German outpatient centres. Data from a clinical registry – TLK Registry, Onkologie 34 (suppl. 6) (2011) 153, https://doi.org/10.1159/000333301.
[14] U. von Verschuer, R. Schnell, M.-O. Zahn, J. Eggert, A. Binninger, L. Spring, M. Jänicke, N. Marschner, Cisplatin vs. carboplatin in routine treatment of advanced non-small cell lung cancer – results from the prospective German TLK cohort study, Oncol. Res. Treat. 40 (suppl. 3) (2017) 174.
[15] A. Rossi, M. Di Maio, P. Chiodini, R.M. Rudd, H. Okamoto, D.V. Skarlos, M. Früh, W. Qian, T. Tamura, E. Samantas, T. Shibata, F. Perrone, C. Gallo, C. Gridelli, O. Martelli, S.-M. Lee, Carboplatin- or cisplatin-based chemotherapy in first-line

treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data, JCO 30 (2012) 1692–1698, https://doi.org/10.1200/JCO.2011.40.4905.
[16] G.P. Kalemkerian, W. Akerley, P. Bogner, H. Borghaei, L. Chow, R.J. Downey, L. Gandhi, A.K.P. Ganti, R. Govindan, J.C. Grecula, J. Hayman, R.S. Heist, L. Horn, T.M. Jahan, M. Koczywas, C.A. Moran, H.B. Niell, J. O'Malley, J.D. Patel, N. Ready, C.M. Rudin, C.C. Williams, Small cell lung cancer, J. Compr. Canc. Netw. 9 (2011) 1086–1113, https://doi.org/10.6004/jnccn.2011.0092.
[17] I. Karam, S.Y. Jiang, M. Khaira, C.W. Lee, D. Schellenberg, Outcomes of small cell lung cancer patients treated with cisplatin-etoposide versus carboplatin-etoposide, Am. J. Clin. Oncol. 38 (2015) 51–54, https://doi.org/10.1097/COC.0b013e31828aab2a.
[18] M. Behera, C. Ragin, S. Kim, R.N. Pillai, Z. Chen, C.E. Steuer, N.F. Saba, C.P. Belani, F.R. Khuri, S.S. Ramalingam, T.K. Owonikoko, Trends, predictors and impact of systemic chemotherapy in small cell lung cancer patients between 1985 and 2005, Cancer 122 (2016) 50–60, https://doi.org/10.1002/cncr.29674.
[19] A. Rossi, O. Martelli, M.D. Maio, Treatment of patients with small-cell lung cancer: from meta-analyses to clinical practice, Cancer Treat. Rev. 39 (2013) 498–506, https://doi.org/10.1016/j.ctrv.2012.09.006.
[20] T. Berghmans, A. Scherpereel, A.-P. Meert, V. Giner, J. Lecomte, J.-J. Lafitte, N. Leclercq, M. Paesmans, J.-P. Sculier, A phase III randomized study comparing a chemotherapy with cisplatin and etoposide to a etoposide regimen without cisplatin for patients with extensive small-cell lung cancer, Front. Oncol. 7 (2017), https://doi.org/10.3389/fonc.2017.00217.
[21] P. Goebell, L. Müller, M. Staehler, A. Nusch, M. Münz, M. Koska, M. Jänicke, N. Marschner, Survival data from patients with advanced or metastatic renal cell carcinoma in routine practice differs significantly from clinical trial data – analyses from the German clinical RCC Registry, Eur. Urol. Suppl. 14 (2) (2015) e6, https://doi.org/10.1016/S1569-9056(15)60009-4.
[22] M.E.R. O'Brien, T.-E. Ciuleanu, H. Tsekov, Y. Shparyk, B. Čučeviá, G. Juhasz, N. Thatcher, G.A. Ross, G.C. Dane, T. Crofts, Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer, JCO 24 (2006) 5441–5447, https://doi.org/10.1200/JCO.2006.06.5821.
[23] C.M. Rudin, M.C. Pietanza, T.M. Bauer, N. Ready, D. Morgensztern, B.S. Glisson, L.A. Byers, M.L. Johnson, H.A. Burris, F. Robert, T.H. Han, S. Bheddah, N. Theiss, S. Watson, D. Mathur, B. Vennapusa, H. Zayed, S. Lally, D.K. Strickland, R. Govindan, S.J. Dylla, S.L. Peng, D.R. Spigel, Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study, Lancet Oncol. 18 (2017) 42–51, https://doi.org/10.1016/S1470-2045(16)30565-4.
[24] D. Simos, G. Sajjady, M. Sergi, M.S. Liew, R. Califano, C. Ho, N. Leighl, S. White, Y. Summers, W. Petrcich, P. Wheatley-Price, Third-line chemotherapy in small-cell lung cancer: an international analysis, Clin. Lung Cancer 15 (2014) 110–118, https://doi.org/10.1016/j.cllc.2013.11.003.
[25] W.K. de Jong, N.H.T. ten Hacken, H.J.M. Groen, Third-line chemotherapy for small cell lung cancer, Lung Cancer 52 (2006) 339–342, https://doi.org/10.1016/j.lungcan.2006.02.005.
[26] S.J. Antonia, J.A. López-Martin, J. Bendell, P.A. Ott, M. Taylor, J.P. Eder, D. Jäger, M.C. Pietanza, D.T. Le, F. de Braud, M.A. Morse, P.A. Ascierto, L. Horn, A. Amin, R.N. Pillai, J. Evans, I. Chau, P. Bono, A. Atmaca, P. Sharma, C.T. Harbison, C.-S. Lin, O. Christensen, E. Calvo, Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial, Lancet Oncol. 17 (2016) 883–895, https://doi.org/10.1016/S1470-2045(16)30098-5.
[27] L. Horn, A.S. Mansfield, A. Szczęsna, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam, D.S. Shames, J. Liu, B. Ding, A. Lopez-Chavez, F. Kabbinavar, W. Lin, A. Sandler, S.V. Liu, IMpower133 study group, first-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer, N. Engl. J. Med. 379 (2018) 2220–2229, https://doi.org/10.1056/NEJMoa1809064.