Received: 2 April 2020 | Revised: 10 September 2020 | Accepted: 4 December 2020

DOI: 10.1002/pds.5179

ORIGINAL ARTICLE

WILEY

Systematic evaluation of the efficacy-effectiveness gap of systemic treatments in extensive disease small cell lung cancer

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Funding information
AbbVie NL, Grant/Award Number: SA-002500_van de Garde

Abstract

Purpose: The aim of this study is to assess how clinical outcomes in real-world (effectiveness) correspond to the outcomes in clinical trials (efficacy) of systemic treatments for extensive disease small cell lung cancer (ED SCLC).

Methods: All patients diagnosed with ED SCLC between 2008 and 2014 in six Dutch large teaching hospitals (Santeon network) were identified and followed-up from date of diagnosis until death or end of data collection. For every patient, an efficacy-effectiveness factor (EE factor) was calculated by dividing individual patients' overall survival (OS) by the pooled median OS assessed from clinical trials with the respective treatment.

Results: From 792 diagnosed patients, 568 (72%) started with first-line treatment. Overall, the median EE factor was 0.79 ($P < .001$ from 1.00). Poor performance status (ECOG≥2) and a higher age at diagnosis (age ≥ 65 years) were independent predictors for a lower EE factor. The EE gap was 43% in patients with both age ≥ 65 years and ECOG ≥2 (EE factor 0.57). The mean age and the proportion of patients with ECOG≥2 in real-world were different from those in clinical trials (mean age of 66 versus 62 years, and ECOG≥2 25% versus 17%; both $P < .001$).

Conclusion: OS of patients with ED SCLC treated with systemic therapy in real-world practice is 21% shorter than for patients included in trials. Age at diagnosis and performance status partly explain this gap.

KEYWORDS
effectiveness, efficacy, pharmacotherapy, real-world, small cell lung cancer, survival

1 | INTRODUCTION

Small cell lung cancer (SCLC) is characterized by its rapid growth, high response rate to chemotherapy and early relapse in patients with metastatic disease.[1] SCLC represents 13% of all lung cancer diagnosis in the Netherlands[2] and other countries in the Western world.[1] The majority of patients is diagnosed with extensive disease (ED),[3,4] with limited treatment options and a median overall survival (OS) of less than 10 months when treated with chemotherapy.[1] Platinum-based combination chemotherapy is standard of care in the United States and Europe as first-line treatment; for second-line treatment re-induction or topotecan can be started.[1,5-7]

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The recommendations in the treatment standards mentioned above are conventionally based on clinical trial data, in which patient populations are studied that are not necessarily a reflection of the general population seen in clinical practice.[8] Important patient characteristics predictive for treatment response are often underrepresented in clinical trial populations. Although data from clinical trials provide important evidence of clinical efficacy, the effectiveness in real-world is largely unknown.

In a previous study in non-small cell lung cancer (NSCLC), we found that survival of patients treated with systemic therapy in real-world practice is almost one quarter shorter than for patients included in clinical trials.[9] A recent systematic literature review on real-world effectiveness of SCLC treatments by Povsic et al. suggested that such an efficacy-effectiveness gap is also present in SCLC.[8] However, they also reported a lack of good quality real-world data about outcomes and emphasize the need to examine this further. For example, individual patient data level studies exploring characteristics associated with a possible efficacy-effectiveness gap are missing.

The aim of the present study is to assess the difference between outcomes of systemic treatments for ED SCLC in clinical trials and in real-world practice in a large nationwide cohort of patients with ED SCLC, and to search for explanatory factors that may explain a gap.

KEY POINTS

- We assessed the difference between outcomes of systemic treatments for extensive disease small cell lung cancer (ED SCLC) in clinical trials (efficacy) and in real-world practice (effectiveness).
- An efficacy-effectiveness factor (EE factor) was calculated by dividing individual patients' overall survival (OS) by the pooled median OS assessed from clinical trials with the respective treatment.
- OS of patients with ED SCLC treated with systemic therapy in real-world practice is 21% shorter (EE factor of 0.79) than for patients included in trials.
- Differences in patients' performance status and age partly explain this gap. This should be acknowledged when deciding for treatment together with patients.

2 | METHODS

2.1 | Data source and study participants

This cohort study was conducted using clinical data originating from the Santeon network of seven large (non-university) teaching hospitals in the Netherlands, which serves more than 12% of the Dutch patient population. We used the Santeon Care for Outcome (CfO) registry for identifying all patients diagnosed with ED SCLC between 2008 and 2014, and for collecting patient characteristics. Data on systemic treatment for ED SCLC was derived from individual patient files. Furthermore, the Santeon Farmadatabase (SFD) was used for validation and collecting additional detailed data about systemic treatments. More details on the CfO registry and SFD can be found elsewhere.[9-11]

Study data were collected and managed using REDCap electronic data capture tools[12] hosted at St. Antonius Hospital, Utrecht/Nieuwegein, the Netherlands. This study was approved by a medical research ethics committee (CMO registration number 2018-4338), with need for informed consent being waived because of the retrospective nature of the study and anonymous handling of data.

2.2 | Patient characteristics and systemic treatment per patient

From the CfO registry, we collected the following patient characteristics: date of diagnosis, age at diagnosis, gender, ECOG performance status (PS), separate comorbidities (to calculate Charlson Comorbidity Index [CCI]), and date of death.

Systemic treatment(s) per patient were extracted from both the individual patient files and the prescription data recorded in the SFD, including start and stop dates, number of cycles and dose, and whether it was first, second or further line of treatment. First-line treatment was defined as the initial systemic therapy following date of diagnosis. Switches to another regimen (eg, from cisplatin-etoposide to carboplatin-etoposide) due to toxicity were considered the same line. Second-line treatment was defined as systemic treatment applied after completion of first-line treatment, or discontinuation of first-line treatment because of disease progression. Re-induction treatment (systemic treatment with the same or similar regimen as administered in the previous line, ≥90 days after finishing first-line treatment) for chemo-sensitive patients was considered a subsequent line of treatment.

2.3 | Systematic literature review for reference outcomes

For all first-line treatment regimens in the study population (except rarely applied regimens [<2%] which were coded as "other"), a systematic literature search (up to September 12, 2018) and meta-analysis were conducted to obtain a (pooled) clinical trial (efficacy) result. Exact details of the search in PubMed, Embase, and CENTRAL (Cochrane library) are provided in Appendix S1. Duplicates were identified and removed using RefWorks (RefWorks Web Based Bibliographic Management Software, ProQuest LLC). An article was included if all the following criteria were met: (a) patients diagnosed with SCLC; (b) main article of a phase III randomized trial; (c) intervention under study is one of the first-line regimens identified in our data; (d) patients with extensive/stage IV disease; and (e) OS as

outcome (with data about distribution of survival times). Criteria for exclusion of articles, the eligibility screening of articles, and the method to determine the reference outcome per regimen is described in further detail by Cramer et al.[9] Appendix S2 provides in more detail per regimen the yield of the systematic review and the meta-analysis data.

2.4 | Real-world treatment outcomes

For every individual patient, an OS was calculated using time between start date of systemic treatment and date of death. Patients still alive at January 31, 2018 (date of update from Personal Records Database [BRP]) were censored and given this end of follow-up date as imputed date of death (n = 7). An efficacy-effectiveness factor (EE factor) was calculated for every patient by dividing the individual real-world OS by the reference outcome (OS) from the corresponding first-line regimen. Toxicity was assessed using percentages of patients with dose reductions (<80% of the initial dose), early discontinuation (at least one cycle less than planned for that regimen) and/or treatment switches within lines of treatment as proxy.

2.5 | Statistical analysis

Statistical Software (SPSS version 24 for Windows; IBM, Armonk, New York) was used for statistical analysis. In case of continuous data mean ± SD or median (range) was given, categorical data was analysed using chi-square and continuous data using t-tests and one-way ANOVA when appropriate.

To assess the existence of a significant EE gap overall and per regimen, the distribution of the calculated EE factors was tested relative to 1.0 using the Wilcoxon signed-rank test. Next, a multivariable linear regression analysis was applied after log-transformation of the EE factor to study the association between patient and treatment characteristics and the magnitude of the EE gap. First, an explanatory analysis was performed to study patient characteristics at diagnosis (age, gender, Charlson comorbidity index [CCI], ECOG performance status [PS], histology and year of diagnosis) as potential prognostic factors. In this analysis, missing values were imputed by single stochastic regression imputation (single run with all available characteristics in the model). Second, we examined whether identified determinants were differently distributed between our population and the clinical trial data to support a potential causal relation. The latter was done by standard descriptive statistics. Third, a multivariable analysis was conducted with toxicity and dose intensity related treatment factors (dose reduction, early discontinuation, switches, and no subsequent line of chemotherapy) as possible associated factors with patient characteristics. Finally, to assess the robustness of our main analysis regarding the presence and significance of the EE gap, a sensitivity analysis was done with calculating the main outcome (OS in real-world) not from start of treatment, but based on date of diagnosis.

3 | RESULTS

From 792 diagnosed patients, 568 (72%) started with first-line treatment. Table 1 presents the baseline patient characteristics per systemic first-line treatment regimen. At diagnosis, the mean age of all treated patients was 66 years, 72% had an ECOG PS 0-1 (3% missing data), and comorbidities (CCI > 0) were present in 57% of the patients. Overall, three regimens (carboplatin-etoposide, cisplatin-etoposide, and cyclophosphamide-doxorubicin-etoposide [CDE]) were responsible for 98% of the variety in applied first-line treatments (n = 559 patients). Dose densities were according to the Dutch guidelines.[2] Table 2 outlines the real-world OS, reference OS from clinical trials (range of inclusion periods from 1985 to 2015), and EE factor for these three first-line regimens. For all regimens, the median OS in real-world is shorter than the clinical trial reference median OS. Overall, the distribution of the EE factor is significantly different from a hypothesized median of 1.00 (median EE factor of 0.79; 95% CI 0.68-0.84; $P < .001$), and the median EE factor is <1.00 for all individual treatment regimens (Table 2).

The multivariable regression analysis showed that age at diagnosis (<≥65 years) and a patients' ECOG PS (<≥2) were significantly associated with the magnitude of the EE factor (Table 3). The negative

TABLE 1 Baseline characteristics ED SCLC patients with first-line treatment

	Carboplatin-etoposide	Cisplatin-etoposide	CDE	Other	All treated patients
Patients, n	335	209	15	9	568
Age at diagnosis, median (min-max)	68 (39-88)	64 (42-84)	68 (49-78)	61 (52-87)	66 (39-88)
Male, n (%)	203 (61)	93 (45)	13 (87)	2 (22)	311 (55)
Comorbidities (CCI ≥ 1), n (%)	197 (59)	112 (54)	9 (60)	6 (67)	324 (57)
ECOG PS, n (%)					
0-1	240 (72)	156 (75)	11 (73)	4 (44)	411 (72)
≥2	83 (25)	46 (22)	4 (27)	5 (56)	138 (24)
Missing	12 (4)	7 (3)	0	0	19 (3)

Abbreviations: BSC, best supportive care; CCI, Charlson Comorbidity Index; CDE, cyclophosphamide-doxorubicin-etoposide; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ED SCLC, extensive disease small cell lung cancer.

TABLE 2 OS and EE factor per first-line regimen

	Patients (n)	Median OS real-world	Median OS clinical trials	Median EE factor (95% CI)[a]
Carboplatin-etoposide	335	7.23[b]	9.48[13-21]	0.76[c] (0.68–0.84)
Cisplatin-etoposide	209	8.18[b]	9.43[17,22-41]	0.87[c] (0.76–0.97)
CDE	15	5.62	7.29[42,43]	0.77 (0.19–1.28)
Total	559	7.43[b]	9.32	0.79[c] (0.74–0.86)

Abbreviations: CDE, cyclophosphamide-doxorubicin-etoposide; OS, overall survival (in months).
[a]Calculated 95% CI hold a risk of over estimation because of not including uncertainty in the fixed reference median OS from the clinical trials.
[b]Significantly different (*P*-values <.05) from median OS clinical trials.
[c]Significantly different (*P*-values <.05) from test value 1.00 (one-sample Wilcoxon signed-rank test).

TABLE 3 Univariable and multivariable analysis of potential prognostic patient variables

	Univariate analysis		Multivariate analysis	
Variable	*B*-value	95% CI	*B*-value	95% CI
Age ≥ 65 years	−0.187	−0.274 to −0.100	−0.133	−0.223 to −0.044
Gender	−0.117	−0.205 to −0.030	−0.084	−0.171 to 0.002
ECOG PS ≥2	−0.215	−0.314 to −0.116	−0.172	−0.273 to −0.072
CCI ≥1	−0.112	−0.200 to −0.025	−0.066	−0.154 to 0.021
Year of diagnosis	0.010	−0.013 to 0.032		

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

TABLE 4 Association between proxies for toxicity and patient characteristics

	ECOG PS			Age		
	0-1	≥2	*P*-value	<65 years	≥65 years	*P*-value
Early discontinuation (<4 cycles) (%)	22.0	37.6	<.001	17.9	32.0	<.001
No subsequent line(s) of treatment (%)	56.0	69.5	.005	49.2	67.1	<.001

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

B-values indicate a larger EE gap for patients aged ≥65 and a higher/worse ECOG PS. The EE gap was 9% in patients <65 years (EE factor 0.91, $P = .045$) and 28% in patients with age ≥ 65 years (EE factor 0.72, $P < .001$; n = 319). Furthermore, the EE gap in patients with ECOG 0-1 was 14% (EE factor 0.86, $P < .001$) and 38% in patients with ECOG ≥2 (EE factor 0.62, $P < .001$; n = 141). Both the mean age of patients in real-world and the proportion of patients with ECOG≥2 in real-world were different from those in clinical trials (66 vs 62 years, and 25% vs 17%, respectively; both $P < .001$). For patients aged ≥65 years and ECOG≥2 (n = 104), the EE gap was 43%.

The sensitivity analysis confirmed the robustness of our findings (data not shown). In real-world practice, the median time between date of diagnosis and start date of systemic treatment was 10 days.

Multivariable analysis on proxies for toxicity showed a significant association of both age and ECOG PS with early discontinuation (both $P < .001$) and no subsequent line of chemotherapy (both $P < .001$). Further analysis showed that those proxies for toxicity are more prevalent in patients with ECOG≥2 and aged ≥65 years (Table 4).

4 | DISCUSSION

This study showed that overall the median OS of patients with ED SCLC treated with first-line systemic therapy in real-world practice is 21% shorter than for patients studied in clinical trials (EE factor 0.79, $P < .001$).

To our knowledge, this is the first study that provides a complete overview on the efficacy-effectiveness gap for systemic treatments in a large unselected population of patients diagnosed with ED SCLC. In combination with our previous research on the EE gap in metastatic NSCLC,[9] this finding adds to the conclusion that the existence of a gap is a general phenomenon in patients with stage IV lung cancer, irrespective of the type of lung cancer and the systemic treatment regimen chosen.

The magnitude of the EE gap found in our study is in line with the findings of Povsic et al in their systematic review on real-world effectiveness on SCLC treatments.[8] They referred to a matched comparison analysis, which showed that the OS benefit of treatment in real-world was 16% lower than that predicted from RCT data.[44] Apart

from confirmation, our study also indicates potential explanatory factors. The mean age of patients diagnosed in real-world is almost five years older than in trial populations. This confirms the general thinking that trials select more fit patients with less comorbidities. The risk of comorbidity increases with age, although CCI showed no significant association with the EE factor in the multivariable regression analysis, possibly due to registration difficulties related to the retrospective nature of the data collection. Another factor is the PS of the patients. Many trials are restricted to ECOG PS 0-1 patients but SCLC patients with higher ECOG PS aim for systemic treatment as well in clinical practice because of a high response rate to systemic treatment. The present study clearly shows that OS benefit significantly drops with worse PS. Patients should be informed about this when deciding for treatment. Especially because our study also showed that earlier discontinuation and no further lines of treatment are more prevalent in patients with ECOG≥2.

Strengths of this study are the large unselected patient population diagnosed with ED SCLC in the Netherlands, providing an overview of most applied systemic treatment options and their outcomes in real-world, from a time frame of >7 years, which reduces the risk for bias from variations over time. In addition, this study is based on complete and precise data with a very low number of missing values (only one variable with 3% missing data).

A limitation of this study could be our approach to compare median OS between real-world and clinical trials primarily. An alternative could be a Cox proportional hazards regression, which has many advantages toward identification of characteristics possibly related to the magnitude of the EE gap (eg, possibility to present hazard ratio's). However, this was not feasible because of the unavailability of individual patient data (IPD) from clinical trials. For the calculation of the magnitude of the EE gap, the potential bias hereof is expected to be very small because of only n = 7 survivors at end date of follow-up (thus not being able to censor these patients). However, the absence of IPD also inhibited a multivariable Cox regression in the search for explanatory factors. Unfortunately, IPD from past clinical trials are not available in the public domain for this type of analyses.

Furthermore, a limitation could be that the time frame under study affects the generalizability of our findings to present daily clinical practice, due to the recent introduction of novel treatment options (addition of immunotherapy to chemotherapy). On the other hand, our findings show a relevant EE gap, irrespective of the chemotherapy chosen, which might also extend to chemo-immunotherapy. Future studies capturing more recent years are needed to discover the effectiveness of these new treatment options in routine practice.

In conclusion, our results show that patients with ED SCLC treated in real-world practice have a 21% shorter survival that those in clinical trials. Differences in patients' performance status and age partly explain this gap. These two factors should be acknowledged when deciding for treatment together with patients.

ACKNOWLEDGMENTS

The authors thank M.J. Deenen and E.A.F. Haak for their efforts to complete the hospital pharmacy data.

FUNDING

This study received financial support from AbbVie NL. This funding source had no role in study design; data collection, analysis and interpretation of data; writing of the report; or decision to submit the article for publication.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Fruh M, De Ruysscher D, Popat S, et al. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(Suppl 6):vi99-vi105.
2. Netherlands Comprehensive Cancer Organisation (IKNL). www.cijfersoverkanker.nl (Accessed March 14, 2019).
3. Carney DN. Lung cancer—time to move on from chemotherapy. *N Engl J Med*. 2002;346(2):126-128.
4. Lally BE, Urbanic JJ, Blackstock AW, Miller AA, Perry MC. Small cell lung cancer: have we made any progress over the last 25 years? *Oncologist*. 2007;12(9):1096-1104.
5. Ardizzoni A. Topotecan in the treatment of recurrent small cell lung cancer: an update. *Oncologist*. 2004;9(Suppl 6):4-13.
6. Rudin CM, Ismaila N, Hann CL, et al. Treatment of small-cell lung cancer: American society of clinical oncology endorsement of the American college of chest physicians guideline. *J Clin Oncol*. 2015;33(34):4106-4111.
7. NVALT. Kleincellig longcarcinoom. Landelijke richtlijn, Versie: 1.0. Oncoline; 2011 https://www.oncoline.nl/files/richtlijn_pdf/790/Kleincellig%20longcarcinoom%201.0.pdf.
8. Povsic M, Enstone A, Wyn R, Kornalska K, Penrod JR, Yuan Y. Real-world effectiveness and tolerability of small-cell lung cancer (SCLC) treatments: a systematic literature review (SLR). *PLoS One*. 2019;14(7):e0219622.
9. Cramer-van der Welle CM, BJM P, Schramel F, et al. Systematic evaluation of the efficacy-effectiveness gap of systemic treatments in metastatic nonsmall cell lung cancer. *Eur Respir J*. 2018;52(6):1801100.
10. Peters BJM, Cramer VD, Welle CM, et al. Trends in prescribing systemic treatment and overall survival for non-small cell lung cancer stage IIIB/IV in the Netherlands: 2008-2012. *Cancer Epidemiol*. 2017;51:1-6.
11. van de Garde EMW, Plouvier BC, Fleuren H, et al. Pharmacotherapy within a learning healthcare system: rationale for the Dutch Santeon Farmadatabase. *Eur J Hosp Pharm*. 2019;26(1):46-50.
12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
13. Heigener DF, Manegold C, Jager E, Saal JG, Zuna I, Gatzemeier U. Multicenter randomized open-label phase III study comparing efficacy, safety, and tolerability of conventional carboplatin plus etoposide versus dose-intensified carboplatin plus etoposide plus lenograstim in small-cell lung cancer in "extensive disease" stage. *Am J Clin Oncol*. 2009;32(1):61-64.
14. Hermes A, Bergman B, Bremnes R, et al. Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: a randomized phase III trial. *J Clin Oncol*. 2008;26(26):4261-4267.
15. Jalal SI, Lavin P, Lo G, Lebel F, Einhorn L. Carboplatin and etoposide with or without palifosfamide in untreated extensive-stage small-cell

lung cancer: a multicenter, adaptive, randomized phase III study (MATISSE). *J Clin Oncol*. 2017;35(23):2619-2623.
16. Lee SM, Woll PJ, Rudd R, et al. Anti-angiogenic therapy using thalidomide combined with chemotherapy in small cell lung cancer: a randomized, double-blind, placebo-controlled trial. *J Natl Cancer Inst*. 2009;101(15):1049-1057.
17. Okamoto H, Watanabe K, Kunikane H, et al. Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. *Br J Cancer*. 2007;97(2):162-169.
18. Schmittel A, Sebastian M, Fischer Von Weikersthal L, et al. A German multicenter, randomized phase III trial comparing irinotecan-carboplatin with etoposide-carboplatin as first-line therapy for extensive-disease small-cell lung cancer. *Ann Oncol*. 2011;22(8):1798-1804.
19. Seckl MJ, Ottensmeier CH, Cullen M, et al. Multicenter, phase III, randomized, double-blind, placebo-controlled trial of pravastatin added to first-line standard chemotherapy in small-cell lung cancer (LUNGSTAR). *J Clin Oncol*. 2017;35(14):1506-1514.
20. Sekine I, Okamoto H, Horai T, et al. A randomized phase III study of single-agent amrubicin vs. carboplatin/etoposide in elderly patients with extensive-disease small-cell lung cancer. *Clin Lung Cancer*. 2014;15(2):96-102.
21. Socinski MA, Smit EF, Lorigan P, et al. Phase III study of pemetrexed plus carboplatin compared with etoposide plus carboplatin in chemotherapy-naive patients with extensive-stage small-cell lung cancer. *J Clin Oncol*. 2009;27(28):4787-4792.
22. Artal-Cortes A, Gomez-Codina J, Gonzalez-Larriba JL, et al. Prospective randomized phase III trial of etoposide/cisplatin versus high-dose epirubicin/cisplatin in small-cell lung cancer. *Clin Lung Cancer*. 2004;6(3):175-183.
23. Berghmans T, Scherpereel A, Meert AP, et al. 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*. 2017;7:217.
24. Eckardt JR, von Pawel J, Papai Z, et al. Open-label, multicenter, randomized, phase III study comparing oral topotecan/cisplatin versus etoposide/cisplatin as treatment for chemotherapy-naive patients with extensive-disease small-cell lung cancer. *J Clin Oncol*. 2006;24(13):2044-2051.
25. Fink TH, Huber RM, Heigener DF, et al. Topotecan/cisplatin compared with cisplatin/etoposide as first-line treatment for patients with extensive disease small-cell lung cancer: final results of a randomized phase III trial. *J Thorac Oncol*. 2012;7(9):1432-1439.
26. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol*. 2006;24(13):2038-2043.
27. Kim DW, Kim HG, Kim JH, et al. Randomized phase III trial of irinotecan plus cisplatin versus etoposide plus cisplatin in chemotherapy-naive Korean patients with extensive-disease small cell lung cancer. *Cancer Res Treat*. 2019;51(1):119-127.
28. Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol*. 2009;27(15):2530-2535.
29. Loehrer PJ Sr, Ansari R, Gonin R, et al. Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: a Hoosier Oncology Group study. *J Clin Oncol*. 1995;13(10):2594-2599.
30. Niell HB, Herndon JE 2nd, Miller AA, et al. Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. *J Clin Oncol*. 2005;23(16):3752-3759.
31. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med*. 2002;346(2):85-91.
32. Oh IJ, Kim KS, Park CK, et al. Belotecan/cisplatin versus etoposide/cisplatin in previously untreated patients with extensive-stage small cell lung carcinoma: a multi-center randomized phase III trial. *BMC Cancer*. 2016;16:690.
33. Pujol JL, Daures JP, Riviere A, et al. Etoposide plus cisplatin with or without the combination of 4′-epidoxorubicin plus cyclophosphamide in treatment of extensive small-cell lung cancer: a French Federation of Cancer Institutes multicenter phase III randomized study. *J Natl Cancer Inst*. 2001;93(4):300-308.
34. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol*. 1992;10(2):282-291.
35. Rowland KM Jr, Loprinzi CL, Shaw EG, et al. Randomized double-blind placebo-controlled trial of cisplatin and etoposide plus megestrol acetate/placebo in extensive-stage small-cell lung cancer: a North Central Cancer Treatment Group study. *J Clin Oncol*. 1996;14(1):135-141.
36. Shi Y, Hu Y, Hu X, Li X, Lin L, Han X. Cisplatin combined with irinotecan or etoposide for untreated extensive-stage small cell lung cancer: A multicenter randomized controlled clinical trial. *Thorac Cancer*. 2015;6(6):785-791.
37. Sun Y, Cheng Y, Hao X, et al. Randomized phase III trial of amrubicin/cisplatin versus etoposide/cisplatin as first-line treatment for extensive small-cell lung cancer. *BMC Cancer*. 2016;16:265.
38. Sundstrom S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol*. 2002;20(24):4665-4672.
39. Tiseo M, Boni L, Ambrosio F, et al. 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*. 2017;35(12):1281-1287.
40. Zatloukal P, Cardenal F, Szczesna A, et al. A multicenter international randomized phase III study comparing cisplatin in combination with irinotecan or etoposide in previously untreated small-cell lung cancer patients with extensive disease. *Ann Oncol*. 2010;21(9):1810-1816.
41. Zhang J, Qi HW, Zheng H, et al. Etoposide-cisplatin alternating with vinorelbine-cisplatin versus etoposide-cisplatin alone in patients with extensive disease combined with small cell lung cancer. *Asian Pac J Cancer Prev*. 2014;15(10):4159-4163.
42. de Jong WK, Groen HJ, Koolen MG, et al. Phase III study of cyclophosphamide, doxorubicin, and etoposide compared with carboplatin and paclitaxel in patients with extensive disease small-cell lung cancer. *Eur J Cancer*. 2007;43(16):2345-2350.
43. Postmus PE, Scagliotti G, Groen HJ, et al. Standard versus alternating non-cross-resistant chemotherapy in extensive small cell lung cancer: an EORTC Phase III trial. *Eur J Cancer*. 1996;32A(9):1498-1503.
44. Lakdawalla DN, Shafrin J, Hou N, et al. Predicting real-world effectiveness of cancer therapies using overall survival and progression-free survival from clinical trials: empirical evidence for the ASCO value framework. *Value Health*. 2017;20(7):866-875.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Cramer-van der Welle CM, Schramel FMNH, Peters BJM, et al. Systematic evaluation of the efficacy-effectiveness gap of systemic treatments in extensive disease small cell lung cancer. *Pharmacoepidemiol Drug Saf*. 2021;30:445–450. https://doi.org/10.1002/pds.5179