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ORIGINAL RESEARCH ARTICLE

Comparative Effectiveness of Lurbinectedin for the Treatment of Relapsed Small Cell Lung Cancer in the Post-Platinum Setting: A Real-World Canadian Synthetic Control Arm Analysis

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Abstract

Background Based on findings from a single-arm, phase 2 basket trial (NCT02454972), lurbinectedin may be an effective treatment for individuals with small cell lung cancer (SCLC) who progressed on or after platinum-based chemotherapy.

Objective To estimate the comparative effectiveness of lurbinectedin versus the historical standard of care for relapsed SCLC in Canada.

Methods A synthetic control arm (SCA) analysis was conducted using real-world data. Population-level data were obtained from real-world databases in Alberta, Canada. Individuals diagnosed with SCLC who initiated post-platinum systemic therapy and met approximated eligibility criteria from the lurbinectedin trial were included in the SCA. Median overall survival (OS) in the SCA was estimated after adjusting for chemotherapy-free interval (CTFI; < 90 versus ≥ 90 days) and stage at initial diagnosis (extensive versus limited). The CTFI-adjusted hazard ratio was estimated using a Cox proportional hazards model.

Results One hundred seventy-four individuals were included in the SCA and 105 in the lurbinectedin trial. The adjusted median OS in the SCA was 6.1 months (95% CI 5.4–7.7 months; unadjusted: 6.7 months, 95% CI 6.0–7.7 months) versus 9.3 months (95% CI 6.3–11.8 months) in the lurbinectedin trial. The adjusted hazard ratio comparing lurbinectedin with the historical standard of care (referent group) was 0.61 (95% CI 0.45–0.82; unadjusted HR: 0.72; 95% CI 0.54–0.97). The hazard ratio was more pronounced among individuals with CTFI ≥ 90 days (HR: 0.49, 95% CI 0.33–0.73).

Conclusion These findings suggest improved OS with lurbinectedin monotherapy versus the historical standard of care in Alberta, Canada.

Key Points

There is currently an absence of randomized clinical trial data assessing the comparative effectiveness of lurbinectedin monotherapy versus the historical standard of care for small cell lung cancer (SCLC) in the post-platinum setting.

In this synthetic control arm analysis of 174 individuals who received treatment in a Canadian real-world setting and who met approximated eligibility criteria from a single-arm lurbinectedin trial ($n = 105$), lurbinectedin was associated with improved overall survival (hazard ratio: 0.61, 95% CI 0.45–0.82), particularly among individuals with a chemotherapy-free interval ≥ 90 days (HR: 0.49, 95% CI 0.33–0.73).

Lurbinectedin may provide a survival benefit over the historical standard of care in relapsed SCLC.

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1 Introduction

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancer diagnoses and is characterized by poor clinical outcomes [1, 2]. Nearly two-thirds of SCLC cases present with extensive-stage (ES) disease and less than 10% are expected to survive beyond 5 years [1, 2].

Treatment of SCLC has not changed substantially over the last two decades. Systemic therapy alone or in combination with radiation therapy are the primary forms of treatment [3–6]. First-line systemic therapy typically consists of cisplatin or carboplatin combined with etoposide and recently with an immunotherapy [3–6] such as atezolizumab (IMPOWER 133) [7] or durvalumab (CASPIAN) [8]. However, the majority of patients will experience disease progression within 1 year of initial therapy [9]. Treatment options following progression in SCLC have historically been limited to rechallenging patients with platinum-based chemotherapy for those with platinum-sensitive disease, or other regimens including topotecan, irinotecan, or cyclophosphamide, doxorubicin and vincristine (CAV) combination therapy for those with platinum-resistant disease [3–6].

In 2020, a single-arm phase 2 basket trial (NCT02454972) suggested that lurbinectedin monotherapy may be an effective treatment in the post-platinum SCLC setting [10]. Among the 105 individuals included in the trial, the overall response rate was 35%, the median duration of response was 5.3 months, and the median overall survival (OS) was 9.3 months [10]. Individuals with a chemotherapy-free interval (CTFI) $\geq$ 90 days seemed to particularly benefit from lurbinectedin therapy with a median OS of 11.9 months versus 5.0 months for individuals with a CTFI < 90 days [10]. The safety profile of lurbinectedin was acceptable and manageable, with the most common grade 3–4 adverse events being hematological [10]. On the basis of these findings, lurbinectedin received accelerated approval from the Food and Drug Administration (FDA) on 15 June 2020 [11].

In 2022, a phase 3 randomized trial assessed lurbinectedin plus doxorubicin versus physician's choice of topotecan or CAV (ATLANTIS, NCT02566993) [12]. The median OS for lurbinectedin plus doxorubicin (8.6 months; $n = 307$) was not significantly different from that of the comparator group (7.6 months; $n = 306$; HR: 0.97; 95% CI 0.82–1.15) [12]. In comparison with the single-arm phase 2 basket trial (NCT02454972), however, lurbinectedin was administered at a lower dose (2.0 mg/m^2). [10, 12] A phase 3 confirmatory study evaluating the effect of lurbinectedin monotherapy at a dose of 3.2 mg/m^2 relative to lurbinectedin in combination with irinotecan or investigator's choice of topotecan or irinotecan therapy is currently underway (LAGOON, NCT05153239) [13].

Since the results from the LAGOON trial are currently unavailable and the ATLANTIS trial reported no survival benefit with lurbinectedin combination therapy, there is uncertainty regarding the comparative effectiveness of lurbinectedin monotherapy versus the historical standard of care. To help address this uncertainty and inform medical decision-making in the interim, we conducted a synthetic control arm (SCA) analysis using real-world data from Alberta, Canada.

2 Methods

2.1 Synthetic Control Arm (SCA)

The Alberta Cancer Registry was used to identify individuals aged 18 years or older diagnosed with SCLC (any stage) between 2004 and 2019 in Alberta, Canada, as well as their corresponding patient demographics and tumor characteristics. Data on comorbidity, emergency room visits, and hospitalizations were assessed using the Discharge Abstract Database (DAD), the National Ambulatory Care Reporting System (NACRS) database, and the Practitioner Claims database. Treatment patterns were captured using provincial electronic medical records. Information on covariates not available in the administrative datasets including the Eastern Cooperative Oncology Group (ECOG) performance status, smoking history, presence of bulky disease, receipt of prophylactic cranial irradiation, and development of brain metastases postdiagnosis were extracted from the medical charts by trained clinicians. Information from these databases were linked using unique lifetime identifiers, which are assigned to all residents of Alberta, Canada.

The front-line systemic therapy regimen was defined according to all agents received within 30 days of initiating the first systemic agent dispensed on or after the date of initial diagnosis. Individuals were flagged as having initiated a subsequent line of systemic therapy based on the earliest of the following two criteria: (1) "switched to a new regimen" defined as receipt of any systemic agent not within the initial regimen (switches from cisplatin to carboplatin and vice versa were not classified as a new line of therapy since they are considered clinically synonymous) or (2) "rechallenged with the same regimen" defined as a gap of more than 60 days between successive treatment dispensations. The regimen of the subsequent line of therapy was classified according to all agents received within 30 days of initiating the subsequent line of therapy.

Individuals who initiated post-platinum systemic therapy and who met approximated eligibility criteria from the lurbinectedin trial were included in the SCA [10]. Specifically, individuals who initiated post-platinum therapy were excluded if they met any of the following criteria: (1) less

than 3 weeks since the last cycle of systemic therapy, (2) brain metastases prior to the time of initiating post-platinum therapy, (3) a cancer diagnosis within 5 years prior to the initial date of being diagnosed with SCLC, (4) any serious adverse events operationalized as any hospitalization or emergency room visit while on prior platinum therapy, (5) human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) within 1 year prior to initiating post-platinum therapy, (6) cardiovascular disease within 1 year prior to initiating post-platinum therapy, (7) receipt of radiation therapy within 2 weeks prior to initiating post-platinum therapy, and (8) ECOG score of three or greater at the time of initiating post-platinum therapy. The International Classification of Diseases (ICD) codes described in Quan et al. (2005) were used to identify prior cancer diagnosis, cardiovascular disease, and HIV/AIDS [14].

2.2 Lurbinectedin Trial

Between 16 October 2015 and 15 January 2019, 105 SCLC patients were enrolled into the lurbinectedin phase 2 basket trial, the details of which have been previously described [10]. Briefly, lurbinectedin monotherapy (at a dose of 3.2 mg/m^2) was administered as an intravenous infusion given once every 3 weeks until disease progression or unacceptable toxicity. Patients defined as both platinum resistant (chemotherapy-free interval, CTFI $<$ 90 days) and platinum sensitive (CTFI $\geq$ 90 days) were included. Complete individual-level data was not available for the lurbinectedin trial at the time of these analyses. Instead, individual-level CTFI-specific survival data from the lurbinectedin trial were abstracted from Kaplan–Meier curves published in the supplementary information of Trigo et al. (2020) using DigitizeIt software [10, 15].

2.3 Study Outcome and Follow-Up

The primary outcome of interest for the SCA analysis was overall survival (OS), as measured from initiation of the post-platinum therapy until the time of death from any cause for both the SCA and lurbinectedin trial arm. Individuals in the SCA were followed from initiation of post-platinum therapy until death, last encounter with the cancer system, or 31 December 2020, whichever occurred first.

2.4 Statistical Methods

Relevant baseline characteristics for the lurbinectedin trial and the SCA were compared using absolute standardized differences (ASDs) [16]. ASD values less than 0.1 are generally thought to approximate the balance achieved in a randomized clinical trial [16].

Kaplan–Meier curves were estimated. Unadjusted median OS as well as the 6 month and 12 month survival were reported along with 95% confidence intervals.

With respect to potential confounders, the following variables were controlled for via restriction by the eligibility criteria: (1) time since last treatment; (2) presence of brain metastases; (3) prior diagnoses of cancer, HIV/AIDS, or CVD; (4) prior radiation therapy; and (5) performance status (partially with respect to the exclusion of individuals with an ECOG score $\geq$ 3). Based on a priori clinical input from three medical oncologists who treat SCLC in Canada, the two most important prognostic factors to control for in the analyses were chemotherapy-free interval (CTFI) and stage at initial diagnosis. Other potential confounders included age, performance status, sites of metastasis, best response to prior systemic therapy, type of prior systemic therapy, and presence of paraneoplastic syndrome.

As done in a prior SCA analysis, median OS as well as 6 month and 12 month survival in the SCA were estimated after re-weighting the SCA to match the distribution of CTFI ($<$ 90 versus $\geq$ 90 days) and stage at initial diagnosis [extensive stage (ES) versus limited stage (LS)] in the lurbinectedin trial [17]. Specifically, four strata corresponding to categories of CTFI and stage at initial diagnosis were defined: (1) CTFI $<$ 90 days and ES, (2) CTFI $<$ 90 days and LS, (3) CTFI $\geq$ 90 days and ES, and (4) CTFI $\geq$ 90 days and LS. The CTFI and stage adjusted survival for the SCA was estimated by taking a weighted sum of the stratum-specific estimates whereby the weights corresponded to the proportion of individuals in the lurbinectedin trial within each stratum [17]. The 95% confidence intervals for the CTFI and stage-adjusted survival estimates were obtained using bootstrapping via the percentile method with 1000 iterations. Due to the lack of strata-specific cell counts available for other combinations of variables in the lurbinectedin trial and the limited sample size, we were unable to explore adjustments for alternative sets of potential confounders in these analyses.

The association between OS and the initiation of lurbinectedin versus the standard of care was quantified using a hazard ratio (HR) estimated from a Cox proportional hazards model. Outcome regression was used to adjust for CTFI in the analyses. Other potential confounders could not be considered in these analyses due to the lack of complete individual-level survival data from the lurbinectedin trial. Subgroup analyses were also conducted within strata defined by CTFI. Since Kaplan–Meier curves for the four strata corresponding to both CTFI and disease stage categories were not available for the lurbinectedin trial at the time of publication, stage at initial diagnosis could not be controlled for at the individual level.

2.5 Quantitative Bias Analysis

A quantitative bias analysis was conducted to assess the potential impact of residual confounding. With respect to residual confounding by stage at initial diagnosis and performance score, a bias-adjusted hazards ratio was estimated via the method described in Lin et al. (1998) using the CTFI-adjusted HR for stage (ES versus LS) and ECOG score (2 versus 0–1) estimated in the SCA and the prevalence of ES disease and ECOG level 2 reported in the SCA and lurbinectedin trial [18]. E-values were also estimated to assess the magnitude of confounding required to fully account for the observed association [19].

2.6 Sensitivity Analyses

Sensitivity analyses were conducted to assess robustness of results to alternative modeling strategies. The primary analysis was repeated after restricting the SCA to either (1) a contemporaneous cohort whereby individuals were included if they initiated post-platinum therapy between October 2015 and January 2019, (2) a cohort including only individuals who received platinum plus etoposide as post-platinum therapy, or (3) to individuals within the age range observed in the lurbinectedin trial (i.e., 54–68 years). Instead of using outcome regression to adjust for CTFI, analyses were also repeated using inverse probability of treatment weighting (IPTW) to estimate the average treatment effect (ATE) and inverse odds weighting to estimate the average treatment effect in the treated (ATT). Within these analyses, robust variance estimation was used to account for the estimation of the treatment weights. The weights were also used to generate CTFI-adjusted Kaplan–Meier curves.

2.7 Ethics and Software

This study was approved by the Health Research Ethics Board of Alberta Cancer Committee (HREBA.CC.22.189; approved July 10, 2022). Analyses were conducted using R version 4.1.0.

3 Results

In total, 3721 individuals were diagnosed with SCLC during the study period in Alberta, Canada. Of these, 2031 (54.6%) initiated platinum-based chemotherapy. Only 577 (28.4%) individuals received a post-platinum systemic therapy, of which 174 (30%) were eligible for inclusion into the SCA (Fig. 1). Among individuals included in the SCA, the mean age at initiation of post-platinum therapy was 65 years (SD: 8.8), 85 (49%) were male, 100 (58%) had ES disease at initial diagnosis, 145 (93%) had a CTFI ≥ 90 days, and the majority had only one prior line of therapy with less than ten individuals having had two prior lines of therapy (Table 1).

There were notable imbalances between the SCA and the lurbinectedin trial population (Table 1). Individuals in the SCA were more likely to be older at initiation of post-platinum therapy (ASD: 0.77), have a CTFI ≥ 90 days (ASD: 0.60), have LS disease at initial diagnosis (ASD: 0.25), and have an ECOG of 2 versus 0–1 (ASD: 0.22). The proportion of individuals who had bulky disease or who received prophylactic cranial irradiation was comparable between the two groups (ASD < 0.1).

In the prior-platinum setting, an approximately equal proportion of individuals in the SCA received carboplatin plus etoposide (44%) versus cisplatin plus etoposide (56%). The post-platinum regimen in the SCA primarily consisted of platinum plus etoposide [carboplatin (54%), cisplatin (18%)]. Within the SCA, 25% of individuals (44/174) initiated a subsequent line of therapy after the post-platinum line, compared with 45% (47/105) in the lurbinectedin trial [20].

During the follow-up period, 164 deaths were observed in the SCA ($n = 174$) compared with 66 in the lurbinectedin trial ($n = 105$) (Fig. 2, Table 2) [10]. The median duration of follow-up was 6.7 months for the SCA and 17.1 months for the lurbinectedin trial. Median OS in the lurbinectedin trial was 9.3 months (95% CI 6.3–11.8 months), which was greater than that of the SCA at 6.7 months (95% CI 6.0–7.7 months). After re-weighting the SCA to match the distribution of CTFI and stage observed in the trial, the median OS in the SCA was 6.1 months (95% CI 5.4–7.7 months).

The CTFI-adjusted hazard ratio comparing the lurbinectedin trial with the SCA (referent group) was 0.61 (95% CI 0.45–0.82; unadjusted HR: 0.72; 95% CI 0.54–0.97; Supplementary Table 1). In a subgroup analysis, the hazard ratio was more pronounced among individuals with CTFI ≥ 90 days ($n = 205$; HR: 0.49, 95% CI 0.33–0.73) than among those with a CTFI < 90 days ($n = 74$; HR: 0.88, 95% CI 0.53–1.44) (Supplementary Table 2, Fig. 3).

A quantitative bias analysis suggested that the magnitude of association would not be meaningfully different after additional adjustment for disease stage at initial diagnosis (HR: 0.59, 95% CI 0.44–0.79) or ECOG score at initiation of post-platinum therapy (HR: 0.62; 95% CI 0.46–0.83). Individual-level data from the SCA was used to estimate the bias parameter for the CTFI-adjusted HR comparing ES versus LS disease (HR: 1.30, 95% CI 0.94–1.79) and ECOG 2 versus 0–1 (HR: 1.30; 95% CI 0.83–2.04). The e-value for the adjusted HR was 2.16 and was 1.82 for the unadjusted HR.

In sensitivity analyses, the estimated hazard ratio was similar when restricting the SCA to a contemporaneous cohort ($n = 44$, HR: 0.67, 95% CI 0.44–1.01), to individuals who received platinum plus etoposide for post-platinum therapy ($n = 126$, HR: 0.58, 95% CI 0.41–0.82), or

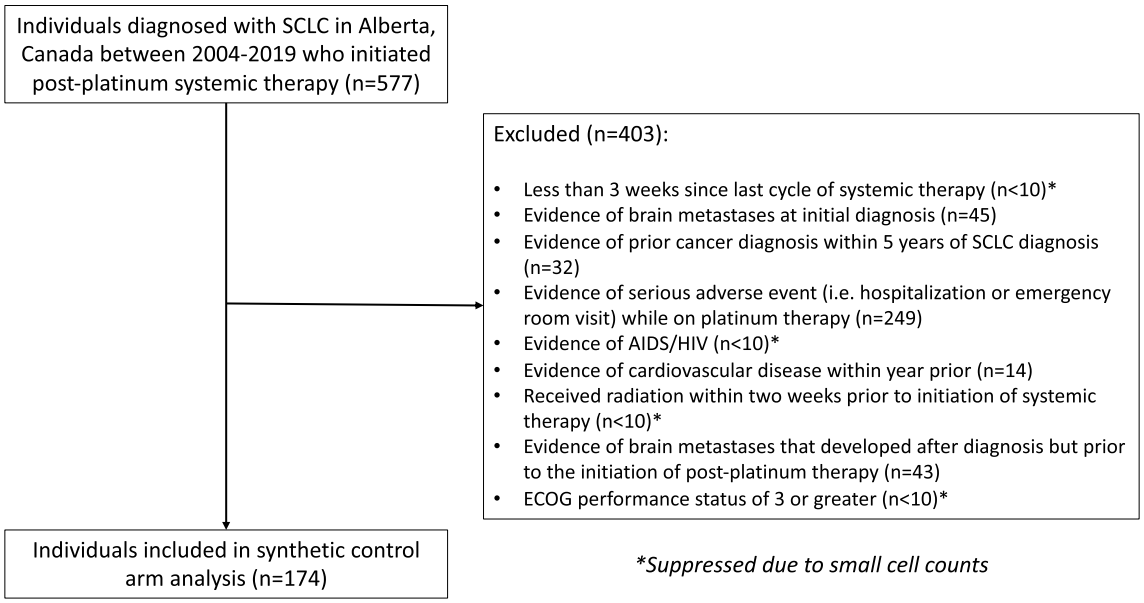

Fig. 1 Flow diagram describing the inclusion of individuals diagnosed with small cell lung cancer (SCLC) in Alberta, Canada between 2004 and 2019 who initiated post-platinum therapy into the synthetic control arm

Table 1 Baseline characteristics of individuals diagnosed with SCLC in Alberta, Canada between 2004 and 2019 who initiated post-platinum therapy and were included in the synthetic control arm (SCA) compared with those in lurbinectedin trial arm

Variable	SCA[a]	Lurbinectedin trial	ASD
n	174	105	–
Male (%)	85 (48.9)	63 (60.0)	0.22
Age (years) at initiation of post-platinum Tx (mean (SD))	65.14 (8.84)	60.0 (2.3)[b]	0.77
ECOG 0–1 (%)	146 (85.4)	97 (92.4)	0.22
Never smoker (%)	< 10[c]	8 (7.6)	–
Extensive stage at initial diagnosis (%)	100 (57.5)	73 (69.5)	0.25
Bulky disease (%)	51 (30.0)	34 (32.4)	0.05
Prophylactic cranial irradiation (%)	106 (60.9)	61 (58.1)	0.06
CTFI 90+ days (%)	145 (83.3)	60 (57.1)	0.60
Post-platinum regimen (%)		–	–
Carboplatin + etoposide	94 (54.0)	–	–
Cisplatin + etoposide	32 (18.4)	–	–
Other[d]	18 (10.3)	–	–
CAV	17 (9.8)	–	–
Etoposide mono	13 (7.5)	–	–
Front-line carboplatin (versus cisplatin) (%)	77 (44.3)	–	–

ASD absolute standardized difference, *CAV* cyclophosphamide, doxorubicin and vincristine, *CTFI* chemotherapy-free interval, *ECOG* Eastern Cooperative Oncology Group, *SCA* synthetic control arm, *SCLC* small cell lung cancer, *SD* standard deviation

[a]Individuals missing data were excluded from the denominator when estimating percentages. The number of individuals missing data in the SCA is as follows: ECOG ($n = 3$), smoking history ($n = 10$), metastatic sites ($n = 1$), and bulky disease ($n = 4$)

[b]The mean was estimated using the reported median value and the standard deviation was estimated as the range divided by 6 [23]

[c]Suppressed due to data privacy legislation

[d]Includes topotecan ($n < 10$), irinotecan ($n < 10$), and other select therapies

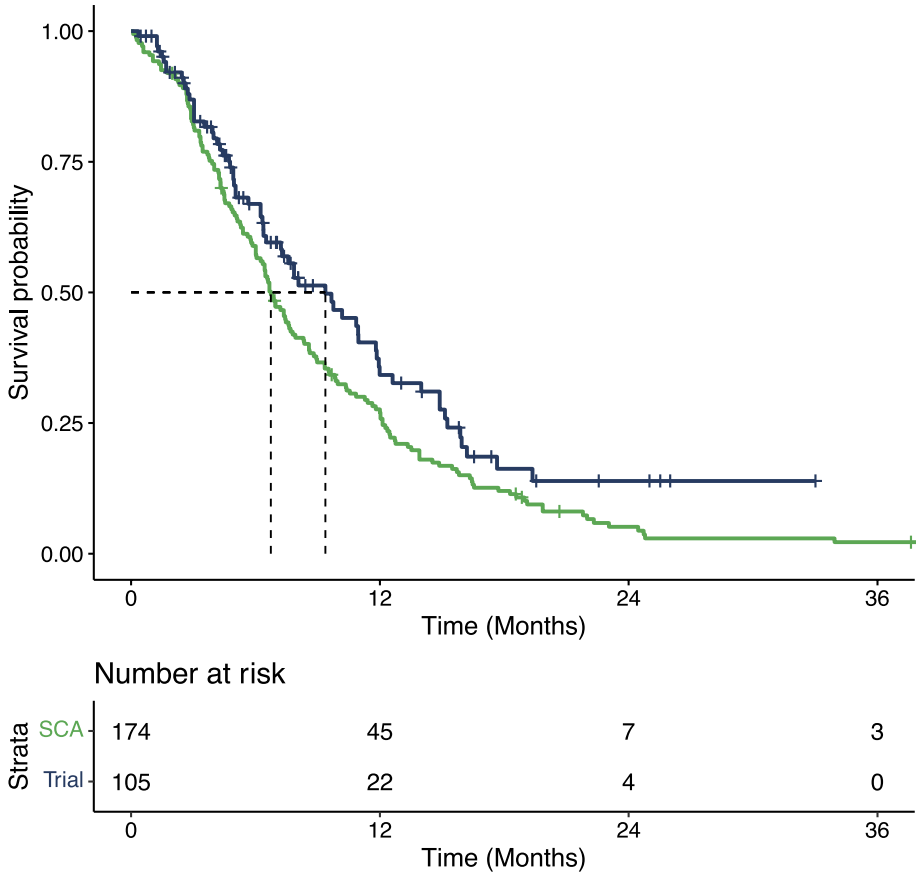

Fig. 2 Kaplan–Meier curves comparing overall survival in the lurbinectedin trial to that of the synthetic control arm

Table 2 Comparison of overall survival (OS) in the lurbinectedin trial (n = 105) and real-world SCA consisting of individuals diagnosed with SCLC in Alberta, Canada between 2004 and 2019 who initiated post-platinum therapy (n = 174)

Statistic	Lurbinectedin trial (95% CI)	SCA unadjusted (95% CI)	SCA adjusted[a] (95% CI)
Median OS (months)	9.3 (6.3–11.8)	6.7 (6.0–7.7)	6.1 (5.4–7.7)
6 month OS (%)	67.1 (57.6–76.7)	58.9 (51.8–65.4)	52.6 (43.9–62.0)
12 month OS (%)	34.2 (23.2–45.1)	27.0 (20.7–33.6)	21.4 (15.7–27.8)

CI confidence interval, *OS* overall survival, *SCA* synthetic control arm, *SCLC* small cell lung cancer

[a]Adjusted for chemotherapy-free interval and stage at initial diagnosis by re-weighting SCA population to match distribution of the trial. The 95% confidence interval was estimated via bootstrapping

to individuals within the observed age range of the trial (n = 86, HR: 0.65; 95% CI 0.45–0.94). Estimates were not meaningfully different when using IPTW (HR: 0.58, 95% CI 0.43–0.79) or inverse odds weighting (HR: 0.64, 95% CI 0.47–0.86) in lieu of outcome regression to control for CTFI (Supplementary Figs. 1 and 2).

4 Discussion

In this study, an SCA analysis was conducted to estimate the comparative effectiveness of lurbinectedin versus the historical standard of care used to treat SCLC in Alberta, Canada, in the post-platinum setting. Our analysis suggests that lurbinectedin may provide a clinically meaningful survival benefit in this patient population. The CTFI-adjusted hazard ratio comparing the lurbinectedin trial to the SCA was 0.61 and was more pronounced among individuals with CTFI ≥ 90 days (HR: 0.49) than among those with a CTFI < 90 days (HR: 0.88). While the strata-specific estimates lacked precision, these findings suggest that the observed survival benefit with lurbinectedin over the historical standard of care was primarily driven by the platinum-sensitive (i.e., CTFI ≥ 90 days) subgroup. The diminished benefit of post-platinum lurbinectedin among those who were platinum-resistant (i.e., CTFI < 90 days) is consistent with prior research reporting

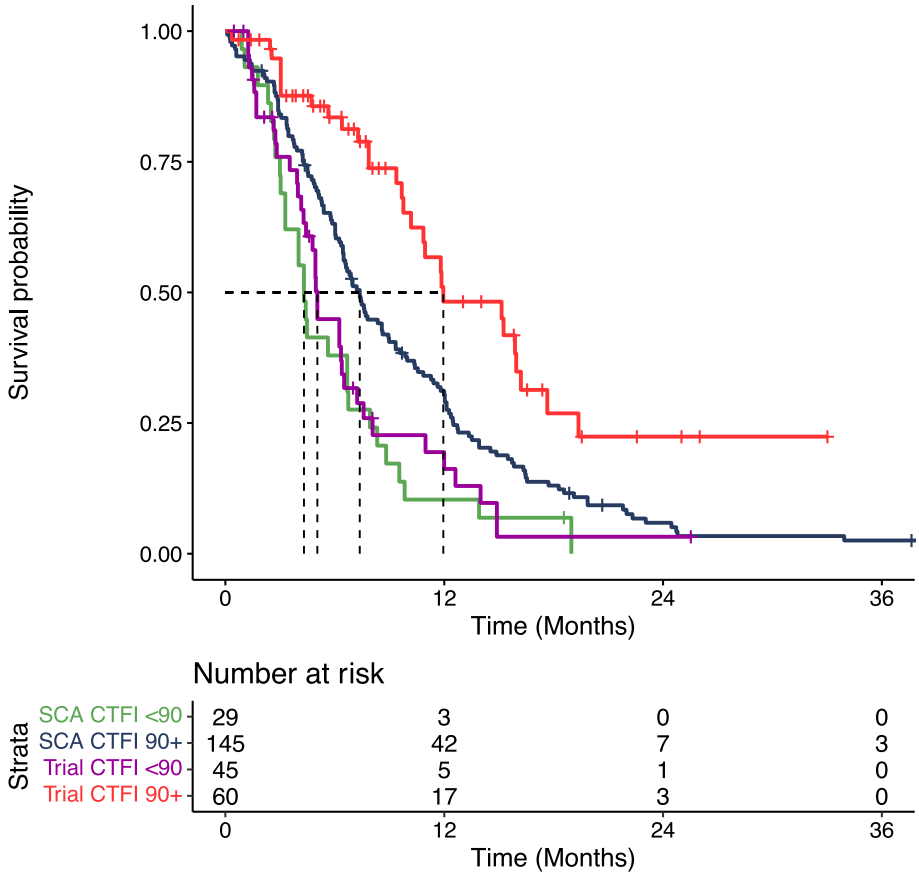

Fig. 3 Kaplan–Meier curves comparing overall survival in the lurbinectedin trial to that of the synthetic control arm stratified by chemotherapy-free interval (CTFI) < 90 days versus ≥ 90 days

lower tumor response rates and worse OS in this subgroup across various types of therapy [21].

Initiated by 127 (72.4%) of the 174 individuals included in our SCA, platinum plus etoposide was the most common form of post-platinum therapy in our comparator group. In contrast, the comparator arm of the LAGOON trial was comprised of topotecan or irinotecan and the ATLANTIS trial used topotecan or CAV [12, 13]. Within our SCA, fewer than ten individuals received either topotecan or irinotecan and only 17 (9.8%) individuals received CAV. Due to the difference in comparator arms, it will not be possible to directly compare these findings with those from the LAGOON trial once available. Instead, an anchored indirect treatment comparison of lurbinectedin versus platinum plus etoposide using data from the LAGOON and other randomized trials is required to confirm our findings [22].

In sensitivity analyses, we found that results from our SCA analysis were robust to alternative modeling strategies. While the findings were similar when using inverse treatment weighting to adjust for CTFI as opposed to outcome regression, the estimated ATT using inverse odds weighting was slightly attenuated compared to the estimated ATE using IPTW. In our SCA analysis, CTFI appeared to modify the association whereby the benefit of post-platinum lurbinectedin appeared to be smaller in the CTFI < 90 days subgroup. The higher proportion of individuals with a CTFI < 90 days in the lurbinectedin trial would therefore explain the attenuation of the ATT since it corresponds to the effect among treated. Notably, the lurbinectedin trial also included platinum-refractory patients ($n = 21$, 21%) who had a CTFI of less than 30 days. Due to our reliance upon an administrative data algorithm to define lines of therapy, the SCA would have excluded individuals with a CTFI of less than 30 days. This exclusion may partially explain the attenuated effect estimate in the platinum-resistant subgroup.

The estimated hazard ratio in the SCA was also slightly attenuated when restricting to a more contemporaneous cohort. While the size of the contemporaneous cohort was small and the estimate was imprecise, this attenuation may be partially due to improvements in OS over time. Specifically, the CTFI- and stage-adjusted HR comparing individuals in the SCA who initiated post-platinum therapy between October 2015 and January 2019 versus individuals who initiated post-platinum therapy between April 2004 and September 2015 was 0.63 (95% CI 0.43–0.93). Despite such improvements in survival over time, the magnitude of association remained clinically meaningful in the contemporaneous cohort (HR: 0.67, 95% CI 0.44–1.01) and was comparable to that of the primary analyses (HR: 0.61, 95% CI 0.45–0.82).

There are important limitations to this investigation. Inherent in any SCA analysis, there is a risk of bias due to residual confounding. Due to the lack of complete individual-level trial data and the limited sample size, we were unable to adjust for covariates other than CTFI in the comparative analyses. With respect to residual confounding by age, stage, and performance status, the results were similar when restricting the SCA to match the age range of the trial and the bias-adjusted estimates for disease stage and ECOG score were similar to those of the primary analysis. Nonetheless, there remains a high risk of bias due to residual confounding from other covariates that were not accounted for in these analyses such as sites of metastasis, best response to prior therapy, and presence of paraneoplastic syndrome. While the e-value of 2.16 suggests that these results are unlikely to be explained away entirely by residual confounding, these findings should be interpreted with caution. Second, we relied on administrative data proxies to define variables such as initiation of post-platinum therapy or serious adverse event on prior platinum therapy, which may have resulted in misclassification. Specifically, the reliance upon administrative data proxies may have resulted in the inclusion of individuals who were still on their initial platinum regimen and the exclusion of individuals who were hospitalized or had an emergency room visit while on prior platinum therapy for reasons other than adverse events. We anticipate that such misclassification would have biased the estimates toward the null value by inflating the observed survival in the SCA. Third, the sample size in the lurbinectedin trial and the SCA were relatively small, which limited the precision of our estimates, particularly within subgroups defined by CTFI. Fourth, we lacked information on response to treatment and disease progression and could not compare these surrogate endpoints between the lurbinectedin trial and SCA. Even if such data were available, however, such comparisons may be unreliable due to differences in how these endpoints are defined and how regularly individuals are monitored for evidence of response or progression in the clinical trial versus the real world. Finally, front-line immunotherapy plus platinum doublet was recently introduced into clinical practice in Canada. Given the time period of our study, no individuals in the SCA received this triplet regimen, which potentially limits the external validity of these findings with respect to the current treatment landscape.

Despite these limitations, there are strengths to this study. First, we relied on population-level cancer registry and electronic medical record data from a single-payer system, which allowed for the identification of individuals with SCLC who initiated platinum therapy with a high degree of accuracy. Second, the majority of individuals in the SCA (94%) were followed until death, which minimizes the risk of bias due to attrition. Lastly, we conducted a chart review to abstract information on covariates not routinely available in administrative data analyses such as performance status, smoking history, and the development of brain metastases postdiagnosis.

5 Conclusions

This SCA analysis using real-world data from Alberta, Canada suggests that lurbinectedin may provide a clinically meaningful survival benefit over the historical standard of care used for the treatment of SCLC in the post-platinum setting, particularly among individuals with a CTFI $\geq$ 90 days. Confirmatory evidence from the ongoing LAGOON trial is needed to verify our results, especially for the CTFI $<$ 90-day subgroup.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-023-00995-1.

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Declarations

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Conflict of Interest Statement Devon J Boyne, Darren R Brenner received consultancy fees from Jazz Pharmaceuticals. Winson Y Cheung consultancy fees from Jazz Pharmaceuticals, AstraZeneca and Janssen. David E Dawe reports honoraria from Jazz Pharmaceuticals, advisory board attendance for Merck Canada, Novartis, Jazz Pharmaceuticals, Pfizer, and AstraZeneca, honoraria for education content from Roche, Boehringer-Ingelheim, and Bristol Myers Squibb, and a research grants from AstraZeneca. Aliyah Pabani received research funding from Bristol Myers Squibb. Cristina Baratta is an employee of and holds stock or stock options in Jazz Pharmaceuticals. Huma Shakir, Ofodile Joe-Uzuegbu, and Eliya Farah declare that they have no conflicts of interest that might be relevant to the content of this manuscript.

Data Availability Statement Data from this investigation are not available for sharing due to provincial data privacy legislation.

Ethics Approval This study was approved by the Health Research Ethics Board of Alberta Cancer Committee (HREBA.CC.22.189; approved 10 July 2022).

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

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nal draft. AP: Conceptualization, methodology, writing—review and editing. CB: Conceptualization, methodology, writing—review and editing. DRB: Data curation, supervision, conceptualization, methodology, writing—review and editing. All authors have read and approved the final version. WYC: Data curation, supervision, conceptualization, methodology, writing—review and editing.

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