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Synthetic Control Arm Analysis of Lurbinectedin Compared to the Standard of Care Among Patients With Small Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy

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Introduction

- Small cell lung cancer (SCLC) is an aggressive subtype of lung cancer that represents 10%–15% of all lung cancer cases[1]
- Outcomes for SCLC are poor with a median survival of <1 year for treated individuals with metastatic disease and <2 years for treated individuals with non-metastatic disease[2,3]
- Immunotherapy in combination with platinum-etoposide chemotherapy is considered the new standard of care (SoC) in the front-line setting. However, when SCLC patients relapse, there are few therapeutic options. In the post-platinum setting, individuals may be rechallenged with platinum plus etoposide or receive CAV (cyclophosphamide, doxorubicin, vincristine) or topotecan[4,5]
- Lurbinectedin, a novel agent that inhibits oncogenic transcription, received conditional approval from Health Canada in September 2021 (for the treatment of adult patients with stage III or metastatic SCLC that has progressed on or after platinum-containing therapy) and represents the first new treatment option in this setting in nearly two decades
- Approval was based on a single-arm, phase 2 trial, in which lurbinectedin demonstrated an overall response of 35.2%, a duration of response of 5.3 months, and a manageable safety profile[6]
- Given the single arm-nature of the study, it is important to better understand the effectiveness of lurbinectedin relative to the current SoC

Objective

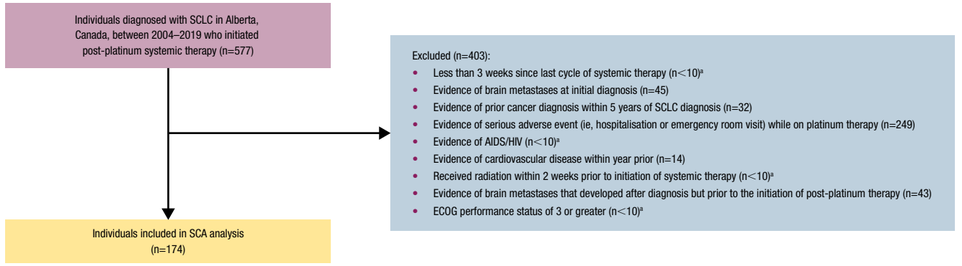
- To conduct a synthetic control arm (SCA) analysis to estimate the comparative effectiveness of lurbinectedin relative to the current SoC among individuals with SCLC previously treated with platinum therapy in Alberta, Canada

Methods

- A SCA was constructed using population-level, real-world data from Alberta, Canada
- Individuals diagnosed with SCLC between 2004–2019 were identified using the provincial cancer registry. Information on relevant covariates and treatments was abstracted from electronic medical records and administrative databases
- Relevant eligibility criteria from the lurbinectedin trial were applied to patients who received platinum-based chemotherapy and initiated a subsequent line of systemic therapy. Individuals who developed brain metastases prior to initiation of post-platinum therapy were excluded
- The distribution of baseline characteristics was compared between the SCA (observed values prior to any adjustment or matching) and the lurbinectedin trial using absolute standardised differences (ASD) whereby values greater than 0.1 typically indicate a meaningful imbalance
- The primary outcome of interest was overall survival (OS) measured from the initiation of post-platinum therapy in the SCA
- Stage at initial diagnosis (extensive stage [ES] vs limited stage [LS]) and the chemotherapy-free interval (CTFI: <90 days vs ⩾90 days) were controlled for in the analyses because these variables were assessed by two senior medical oncologists as the most important prognostic factors in SCLC. Stage- and CTFI-standardised median OS estimates were generated for the SCA, whereby stratum-specific estimates from the SCA were pooled using weights corresponding to the observed distribution of stage and CTFI in the lurbinectedin trial. The 95% confidence interval (CI) for the pooled estimates was generated using bootstrapping
- CTFI-specific Kaplan-Meier (KM) curves were extracted from the lurbinectedin B-005 trial using DigitizeIt software.[7] These data were used to estimate a CTFI-adjusted hazard ratio (HR) using a Cox proportional hazards model (overall and stratified by CTFI)
- In a sensitivity analysis, CTFI-adjusted HR was re-estimated such that the SCA population was directly matched to the trial population based on CTFI instead of using covariate adjustment in the outcome model. A quantitative bias analysis (QBA) was conducted to assess the potential impact of residual confounding by stage at initial diagnosis using the estimated prevalence of ES disease in the trial and SCA as well as the CTFI-adjusted HR comparing ES vs LS in the SCA[8]

Results

Figure 1. Inclusion of Individuals Diagnosed With SCLC in Alberta, Canada, From 2004–2019 Who Initiated Post-Platinum Therapy Into the SCA Analysis



AIDS, acquired immunodeficiency syndrome; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; SCA, synthetic control arm; SCLC, small cell lung cancer.
[a]Suppressed due to small cell counts.

- In total, 3721 individuals were diagnosed with SCLC during the study period, of whom 2031 (55%) initiated platinum therapy. Of the 2031 individuals who initiated platinum therapy, 577 (28%) subsequently initiated a post-platinum systemic therapy regimen. After applying eligibility criteria from the lurbinectedin trial (where possible), 174 (30%) were eligible for inclusion into the SCA

Table 1. Baseline Characteristics of Individuals Included in the SCA Compared to Those in the B-005 Lurbinectedin Trial

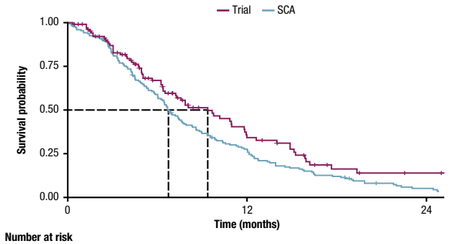
Variable	SCA[a]	Trial	ASD
N	174	105	-
Male, n (%)	85 (48.9)	63 (60.0)	0.22
Age at initiation of post-platinum Tx, mean (SD)	65.1 (8.8)	60.0 (2.3)	0.77
ECOG 0–1, n (%)	146 (85.4)	97 (92.4)	0.22
Never smoker, n (%)	<10[b]	8 (7.6)	-
Extensive stage at initial diagnosis, n (%)	100 (57.5)	73 (69.5)	0.25
Bulky disease, n (%)	51 (30.0)	34 (32.4)	0.05
Prophylactic cranial irradiation, n (%)	106 (60.9)	61 (58.1)	0.06
CTFI ⩾90 days, n (%)	145 (83.3)	60 (57.1)	0.60
Post-platinum regimen, n (%)			
Carboplatin + etoposide	94 (54.0)		
Cisplatin + etoposide	32 (18.4)		
Other[c]	18 (10.3)		
CAV	17 (9.8)		
Etoposide mono	13 (7.5)		
Front-line carboplatin (vs cisplatin), n (%)	77 (44.3)		

ASD, absolute standardised differences; CAV, cyclophosphamide, doxorubicin, vincristine; CTFI, chemotherapy-free interval; ECOG, Eastern Cooperative Oncology Group; SCA, synthetic control arm.
[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]Suppressed due to data privacy legislation.
[c]Includes topotecan, irinotecan, and other select therapies.

- Compared to individuals in the lurbinectedin trial, individuals in the SCA were more likely to be older (ASD: 0.77), female (ASD: 0.22), have an Eastern Cooperative Oncology Group (ECOG) score of 2 vs 0–1 (ASD: 0.22), have LS disease at initial diagnosis (ASD: 0.25), and have a CTFI ⩾90 days (vs <90 days) (ASD: 0.60). Imbalances in disease stage and CTFI suggest individuals in the SCA had a better prognosis compared to individuals in the lurbinectedin trial
- The most common form of systemic therapy used after initial platinum-based therapy was platinum plus etoposide

- In the SCA, the unadjusted median OS was 6.7 months (95% CI: 6.1, 7.8), and, as expected, was higher among individuals with LS disease at diagnosis (7.8 months, 95% CI: 6.1, 12.0) than ES disease at diagnosis (6.6 months, 95% CI: 5.4, 7.5). Median OS was also higher among individuals with CTFI ⩾90 days (7.4 months, 95% CI: 3.3, 6.7) than those with CTFI <90 days (4.3 months, 95% CI: 3.3, 6.7)
- The median OS in the lurbinectedin trial of 9.3 months (95% CI: 6.3, 11.8) was greater than the corresponding CTFI- and stage-standardised estimate from the SCA of 6.1 months (95% CI: 5.4, 7.7)
- In a sensitivity analysis, the CTFI-adjusted HR was not meaningfully different when using direct matching vs outcome regression adjustment (HR: 0.63, 95% CI: 0.45, 0.90; *P*=0.01)
- Regarding the QBA, the estimated prevalence of ES disease was 69.5% in the lurbinectedin trial and 57.5% in the SCA, and the CTFI-adjusted HR comparing ES vs LS disease in the SCA, was 1.30 (95% CI: 0.94, 1.79). Using these estimates as inputs for the QBA, the HR estimate after adjustment for stage was not meaningfully different (HR: 0.59, 95% CI: 0.44, 0.79)

Figure 2. Unadjusted Overall Survival up to 24 Months in the Lurbinectedin B-005 Trial (n=105) and the SCA (n=174)

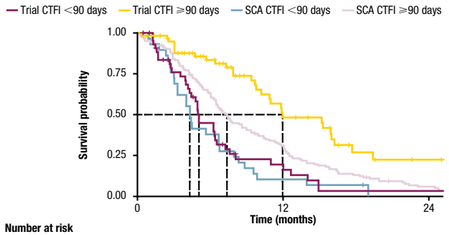


Number at risk			
Strata Trial	105	22	4
Strata SCA	174	45	7

SCA, synthetic control arm.

- The CTFI-adjusted HR comparing lurbinectedin to the SCA was 0.61 (95% CI: 0.45, 0.82; *P*=0.001; unadjusted HR: 0.72, 95% CI: 0.54, 0.97; *P*=0.03)

Figure 3. Unadjusted Overall Survival up to 24 Months in the Lurbinectedin B-005 Trial (n=105) and the SCA (n=174) Stratified by CTFI (<90 vs ⩾90 Days)



Number at risk			
Strata Trial CTFI <90 days	45	5	1
Strata Trial CTFI ⩾90 days	60	17	3
Strata SCA CTFI <90 days	29	3	0
Strata SCA CTFI ⩾90 days	145	42	7

CTFI, chemotherapy-free interval; SCA, synthetic control arm.

- In a subgroup analysis, the HR was larger in magnitude among those with CTFI ⩾90 days (HR: 0.49, 95% CI: 0.33, 0.73; *P*<0.001) than among those with CTFI <90 days (HR: 0.88, 95% CI: 0.53, 1.44; *P*=0.61)

Discussion

- These findings suggest that lurbinectedin may be superior to the current SoC used in Alberta, Canada, among individuals with SCLC in the post-platinum setting, particularly among individuals with a CTFI ⩾90 days
- Strengths:
  - We leveraged a large, population-level database that is less prone to selection bias and more representative of the current SoC than other databases with limited catchment areas
  - We accounted for a number of important eligibility criteria not routinely captured in other administrative data sources such as ECOG performance status or smoking history by conducting a comprehensive medical chart review
  - Due to robust access to vital statistics data, we had a long duration of follow-up and were able to follow the majority of individuals until death
- Limitations:
  - Due to our reliance on published KM data and the limited sample size of the trial and SCA, we were unable to adjust for potential confounders other than CTFI. While the QBA suggested that the results were robust to residual confounding by stage at initial diagnosis, there remains a risk of residual confounding from ECOG and other covariates (both measured and unmeasured)
  - There are systematic differences between the level of care received in a clinical trial and in real-world settings that cannot be fully accounted for in an SCA analysis. As such, these estimates may overestimate the magnitude of effect
  - We relied on administrative data algorithms to define certain eligibility criteria used to identify the cohort, which may have led to misclassification. Since the degree of misclassification would be greater in the SCA than in the trial, there is a risk of bias due to differential misclassification

Conclusions

- There is an unmet need for more effective therapies for SCLC in the post-platinum setting
- These findings suggest potential benefit with initiation of lurbinectedin compared to the SoC in Alberta, Canada, in the post-platinum SCLC setting
- Additional research is needed to confirm these findings and to assess real-world outcomes of individuals treated with lurbinectedin in the post-market setting

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