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*Original Research*

# Efficacy of carboplatin–etoposide rechallenge after first-line chemo-immunotherapy in ES-SCLC: an international multicentric analysis

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***Abstract***

**Background and objectives:** Second-line treatment for small-cell lung cancer (SCLC) is primarily guided by the time elapsed since the last platinum dose. Rechallenge with carboplatin and etoposide has demonstrated superior outcomes compared to topotecan if the platinum-free interval (PFI) is longer than 90 days and is considered the standard of care. However, these findings predate the chemo-immunotherapy era. This study investigates the effectiveness of the rechallenge strategy after chemo-immunotherapy in a real-world setting.

**Design and methods:** We retrospectively reviewed patients with the extensive stage (ES)-SCLC who received rechallenge with carboplatin and etoposide after first-line chemoimmunotherapy between September 2020 and August 2023 in nine European centres. Demographic and clinical data were collected and analysed.

**Results:** A total of 93 patients were included. Sixty-six (71%) patients had a PFI between 3 and 6 months. Consolidation thoracic radiotherapy and prophylactic cranial irradiation had been administered in 31 (33.3%) patients and 20 (21.5%) patients, respectively. Overall response rate was 59.1%. Median progression-free survival (PFS) was 5 months (95% confidence interval (CI) 4.3–5.7) and median overall survival (OS) was 7 months (95% CI 5.7–8.3). Notably, PFS and OS were not different according to PFI (3–6 m vs $>$ 6 m).

**Conclusion:** Rechallenge with carboplatin and etoposide is a valid second-line option in patients with ES-SCLC whose disease progresses after first-line chemoimmunotherapy. Our analysis shows similar results to previous studies. Furthermore, outcomes were consistent across patients with different PFIs, confirming its efficacy in patients with a PFI longer than 3 months.

***Keywords:*** carboplatin and etoposide, chemoimmunotherapy, immunotherapy, rechallenge, small-cell lung cancer

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## Introduction

Small-cell lung cancer (SCLC) is a highly aggressive disease that accounts for 15% of all lung cancer cases.[1] About 70% of patients are diagnosed with an extensive stage (ES), meaning that the tumour cannot be encompassed within a radical radiotherapy field.[2] The first-line standard of care in these patients is the combination of platinum, etoposide and an immune checkpoint inhibitor (ICI) such as atezolizumab or durvalumab.

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Although overall response rates (ORRs) are initially high (60%–80%), all patients will eventually experience disease progression.[3–7]

Second-line treatment options are limited, and regimen choice is based on the platinum-free interval (PFI), defined as the time from the last platinum dose to the first evidence of progressive disease (PD). The cut-off to differentiate between platinum-sensitive and platinum-resistant SCLC has been traditionally established at 90 days.[8] In these patients, rechallenge with carboplatin and etoposide is recommended.[8] Evidence of the efficacy of this regimen was previously based on retrospective, non-randomized trials, showing ORRs over 50%.[9,10]

In 2020, the results of a phase III, open-label, multicentre, randomized trial comparing rechallenge with carboplatin and etoposide versus topotecan were published.[11] Patients with a PFI over 90 days receiving rechallenge with carboplatin and etoposide had a significantly higher ORR (49% vs 29%, $p=0.0024$) and longer progression-free survival (PFS) (4.7 m vs 2.7 m; HR = 0.57; $p=0.0041$) compared to standard topotecan. Overall survival (OS) was not significantly different (7.5 months vs 7.4 months).[11]

Notably, the aforementioned studies precede the chemo-immunotherapy era. Therefore, evidence of the efficacy of rechallenge in platinum-sensitive patients who previously received an ICI is scarce.

Our study aims to shed light on the real-world outcomes of platinum-etoposide rechallenge in patients whose disease progressed after first-line chemo-immunotherapy, with a PFI of at least 90 days. Our main objective was to define the survival outcomes in this population.

## Materials and methods

### *Study design*

We conducted a retrospective, multicentric, non-interventional cohort study in nine European centres. This study was registered and approved as an audit by the multiple participating sites with the coordinating centre being The Christie NHS Foundation Trust in Manchester, UK. Clinical data were anonymized before sharing with the coordinating centre for analysis. The audit procedures were compliant with the precepts of Good Clinical Practice guidelines with regard to the collection, storage, processing and disclosure of personal information and the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. Patient data were collected through an electronic case report form (eCRF) by each provider through medical chart review. Collected data included patient demographics, clinical characteristics at the time of diagnosis/initiation of a given line of therapy and clinical outcomes. The study adheres to the STROBE cohort reporting guidelines[12] (Supplemental File 1).

### *Patients*

Eligible patients were adults aged ⩾18 years at the time of diagnosis who had to meet the following criteria: histologically or cytologically confirmed SCLC; had received first-line palliative treatment with carboplatin/cisplatin, etoposide and atezolizumab/durvalumab; the first subsequent therapy consisted of carboplatin and etoposide; the PFI was at least 90 days; and this treatment was initiated between September 2020 and August 2023. We split the patients into two groups: those with a PFI between 3 and 6 months and those with a PFI longer than 6 months.

### *Outcomes*

Tumour response was evaluated by investigators based on the local radiology report using CT scans according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. A central independent blinded review was not conducted. Disease responses for determining ORR were as reported in the eCRF, including the date of radiological imaging used to substantiate the patient's initial and best response to therapy. ORR was defined as the proportion of patients that had either complete response (CR) or partial response (PR). PFS was calculated as the period elapsed from treatment initiation to radiological progression or death from any cause, whichever occurred first. Patients alive without evidence of PD at the last follow-up were censored. OS was defined as the time from treatment initiation to the date of death.

### *Statistical analysis*

In descriptive statistical analyses, continuous variables are presented as medians and ranges, whereas categorical variables are presented as

**Table 1.** Clinical characteristics are global and according to PFI.

| Variables | Total ($n = 93$) | PFI 3–6 months ($n = 66$) | PFI > 6 months ($n = 27$) | *p* |
|---|---|---|---|---|
| Sex, no. (%) | | | | 0.711 |
| Male | 46 (49.5) | 32 (48.5) | 14 (53.8) | |
| Female | 46 (49.5) | 34 (51.5) | 12 (46.2) | |
| Median age, years (range) | 64 (42–84) | 65 (43–84) | 67 (45–81) | |
| ECOG, no. (%) | | | | 0.503 |
| 0 | 6 (6.5) | 3 (4.5) | 3 (11.1) | |
| 1 | 72 (77.4) | 52 (78.8) | 20 (74.1) | |
| 2 | 15 (16.1) | 11 (16.7) | 4 (14.8) | |
| Smoking status, no. (%) | | | | 0.155 |
| Never smoker | 1 (1.1) | 0 (0.0) | 1 (3.7) | |
| Former smoker | 44 (47.3) | 34 (51.5) | 10 (37.0) | |
| Current smoker | 48 (51.6) | 32 (48.5) | 16 (59.3) | |
| Liver metastases, no. (%) | | | | 0.143 |
| No | 51 (54.8) | 32 (48.5) | 19 (70.4) | |
| Yes | 41 (44.1) | 34 (51.5) | 8 (29.6) | |
| Brain metastases, no. (%) | | | | 0.958 |
| No | 72 (77.4) | 51 (77.3) | 21 (77.8) | |
| Yes | 21 (22.6) | 15 (22.7) | 6 (22.2) | |

ECOG, Eastern Cooperative Oncology Group; PFI, platinum-free interval.

frequencies and percentages. The correlation between variables was evaluated using a simple linear regression model. Comparison between two variables was analysed using a Chi-square test or Fisher's exact test for categorical variables and a Wilcoxon rank-sum test or Pearson's correlation analysis for continuous variables. A *p*-value of less than 0.05 was deemed to indicate statistical significance. For data that were not normally distributed, the median values along with the minimum and maximum values were reported. The variables analysed included gender, age, Eastern Cooperative Oncology Group Performance Status (ECOG PS), stage of disease at initial diagnosis, smoking status, presence of liver or brain metastases before starting rechallenge and platinum sensitivity. Survival analysis was conducted using the Kaplan–Meier method. All analyses were carried out in SPSS Version 24.0 (SPSS Inc., Portsmouth, Hampshire, UK).

## Results

### *Patients*

Clinical and demographic characteristics before initiation of second-line treatment stratified by PFI are shown in Table 1. A total of 93 patients were included in the study with a median age of 64 years (range 42–84) and 46 (49.5%) were females. Sixty-six (71%) patients had a PFI between 3 and 6 months, while 30 (29%) had a PFI longer than 6 months. The best response to the first line of therapy was PR in 84 (90.3%) patients and CR in 4 (4.3%) patients. Consolidation thoracic radiotherapy and prophylactic cranial irradiation were given to 31 (33.3%)

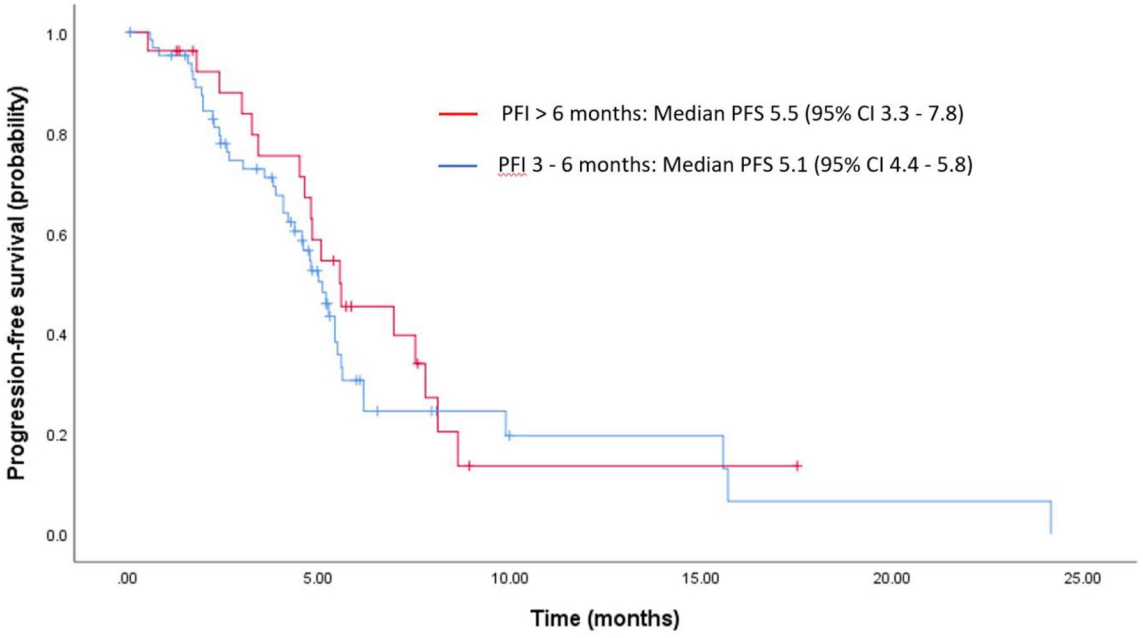


**Figure 1.** Kaplan–Meier curves for progression-free survival in patients with a PFI between 3 and 6 months and >6 months.
PFI, platinum-free interval.

and 20 patients (21.5%), respectively. The median number of rechallenge cycles was 4 (range 1–6).

### *Clinical outcomes*

Most patients ($n=87$, 93.4%) were evaluable for response. Among them, ORR was 58.6%, and disease control rate was 75.9%. Twenty-one (24.1%) patients experienced PD as the best response to rechallenge.

At the time of data cut-off, 61 (65.6%) patients had experienced either disease progression or death. Median follow-up in censored patients was 7.0 (IQR 4.9–11.6) months. The median PFS in the whole population was 5.1 months (95% confidence interval [CI] 4.1–5.7). Median PFS in patients with a PFI of 3 to 6 months and patients with a PFI > 6 months were 5.1 (95% CI 4.4–5.8) and 5.5 (95% CI 3.3–7.8) months, respectively, without a significant difference ($p=0.431$) (Figure 1). The median OS was 7.6 (95% CI 5.9–9.2) months. In patients with a PFI between 3 and 6 months, the median OS was 6.7 (95% CI 6.0–7.4) months while in patients with a PFI > 6 months, it was 8.7 (95% CI 5.6–11.8) months, without significant differences ($p=0.425$) (Figure 2).

Thirty-two (34.4%) patients experienced grade 3 or higher toxicity related to chemotherapy. Dose reductions were reported in 39 (41.9%) patients and treatment was stopped due to toxicity before completing four cycles in 20 (21.5%) patients. Among patients who experienced PD ($n=73$; 78.5%), 29 (39.7%) received a subsequent line of treatment. The most frequent regimens were vincristine, adriamycin and cyclophosphamide ($n=12$; 41.4%).

## Discussion

Most of the studies of second-line therapies in SCLC were conducted before the introduction of ICIs in the treatment armamentarium. The first evidence of a differential response and survival depending on the chemotherapy-free interval (CTFI) was published in the 1980s. In a small sample trial, Giaccone et al. observed that patients with a CTFI longer than 90 days had a higher ORR to a cross-resistant chemotherapy regimen.[13] Subsequently, most second-line trials were designed in patients with a CTFI longer than 90 days[14,15] or 60 days.[16,17] In 2014, Ardizzoni et al. analysed six topotecan-based trials and found that patients with a CTFI shorter than 60 days had poor OS.[18] More recently, lurbinectedin has been approved as a second-line treatment

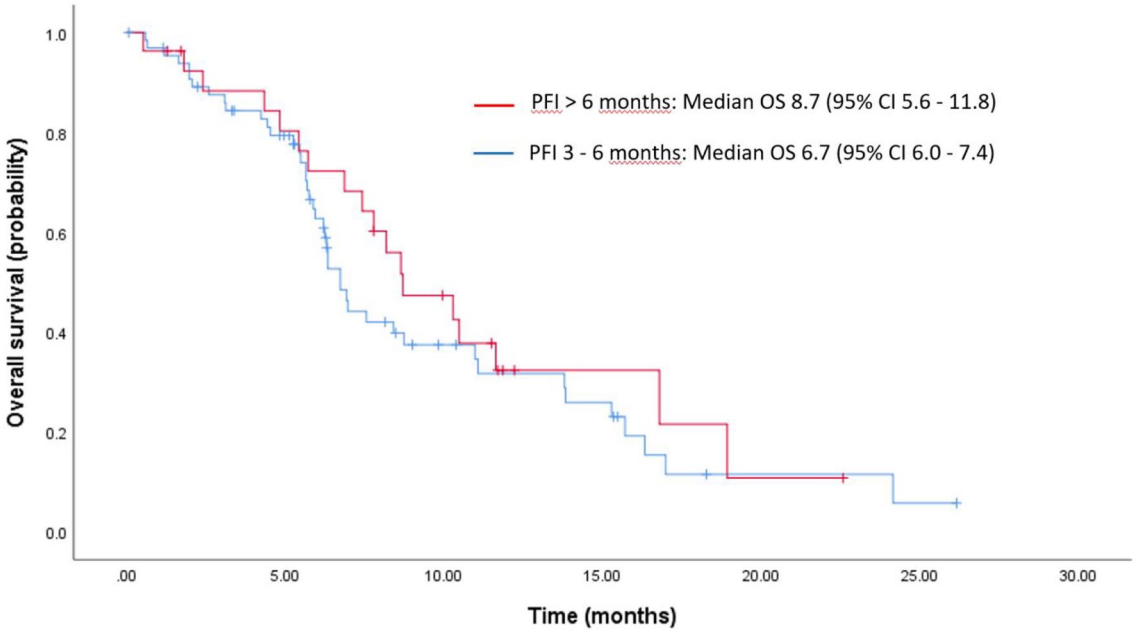


**Figure 2.** Kaplan–Meier curves for overall survival in patients with a PFI between 3 and 6 months and >6 months.
PFI, platinum-free interval.

in the United States based on a phase II, single-arm trial in this setting.[19] A real-world, multicentric study showed that, in patients treated with first-line chemo-immunotherapy, lurbinectedin had a median PFS and OS of 2.5 months (95% CI 1.6–4.7) and 4.5 months (95% CI 3.0–6.8), respectively. In patients with a PFI >90 days, the 6-month PFS with lurbinectedin was 23%.[20] With regard to rechallenge carboplatin and etoposide, a phase III trial showed higher ORR, longer PFS and similar OS compared to topotecan among patients whose PFI is longer than 90 days.[11]

Recently, a retrospective multicentric analysis explored the cut-off value in patients treated with chemotherapy alone or chemo-immunotherapy.[21] In the chemo-immunotherapy cohort ($n = 98$), they showed that 75 days may be a better predictor of subsequent prognosis.[21] Notably, only 16 patients had received platinum rechallenge and all of them had a PFI longer than 75 days.[21] Another Japanese retrospective study of 57 patients treated with first-line chemo-immunotherapy examined the relationship between post-progression survival (PPS) and OS, as well as clinical factors associated with a longer PPS.[22] Most patients ($n = 34$) received second-line amrubicin and only four patients received rechallenge carboplatin and etoposide, but the latter had a significantly longer PPS.[22]

To our knowledge, this is the first study focusing specifically on patients treated with rechallenge carboplatin and etoposide after chemo-immunotherapy. We showed an ORR higher than 50%, a PFS of 7 months and an OS of 7.6 months, which are remarkably similar to the results of the phase III trial published by Baize et al.[11] More importantly, most of our cohort was composed of patients with a PFI between 3 and 6 months ($n = 66$; 71%). Those patients did not have significantly lower survival outcomes compared to patients with a PFI longer than 6 months, and the clinical characteristics were well balanced between the two groups.

Our study has several limitations. Firstly, due to its retrospective nature, patients were not randomly allocated to platinum-based rechallenge, so patients with a better fitness status could have been selected for this regimen. Nevertheless, the clinical characteristics of the cohort seem to be consistent with the published literature, as more than 15% had an ECOG PS of 2. Secondly, disease evaluation was performed according to local practice, which may explain the slightly longer PFS but similar OS compared to the phase III trial published by Baize et al. Thirdly, we only collected patients treated with rechallenge, so the efficacy of other regimens such as topotecan in this population remains uncertain.

Despite these limitations, this is the first study exploring the efficacy of platinum-based rechallenge after chemo-immunotherapy. The results are reassuring and confirm that this regimen continues to be a valid therapeutic alternative in this setting.

## Conclusion

Rechallenge with carboplatin and etoposide represents a valid second-line option for patients diagnosed with ES-SCLC who have progressed following first-line chemo-immunotherapy. Our analysis shows survival outcomes comparable to those observed in studies conducted before the introduction of ICIs in the first-line setting. Notably, there were no significant differences in results between patients with a PFI of 3 to 6 months and those with a PFI longer than 6 months, confirming its efficacy in patients with a PFI longer than 3 months.

## Declarations

### *Ethics approval and consent to participate*

This study was registered and approved as an audit by the multiple participating sites with the coordinating centre being The Christie NHS Foundation Trust in Manchester (UK), project number 3685. Individual consent for this retrospective analysis was waived.

### *Consent for publication*

Not applicable.

### *Author contributions*

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**Sofía Silva Díaz:** Conceptualization; Data curation; Writing – original draft; Writing – review & editing.

**Carles Escriu:** Conceptualization; Data curation; Writing – review & editing.

**Saara Mohammed:** Conceptualization; Data curation; Writing – review & editing.

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### *Competing interests*

The authors declare that there is no conflict of interest.

### *Availability of data and materials*

The data that support the findings of this study are available from the corresponding author, RC, upon reasonable request.

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## Supplemental material

Supplemental material for this article is available online.

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