Systematic Literature Review of Clinical Data in Third-Line and Beyond Therapies in Patients with Small Cell Lung Cancer

Dirnberger F[1], Mayer B[2], Appiah K[3], Rizzo M[2], Suri G[4]

[1]Amgen GmbH, München, Germany, [2]Cytel Inc., London, UK, [3]Cytel, Rotterdam, Netherlands, [4]Amgen Limited, Uxbridge, UK

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INTRODUCTION

- Small cell lung cancer (SCLC) is an extremely aggressive form of cancer that accounts for approximately 15% of all lung cancer cases.[1,2]
- Owing to the aggressive nature of the disease, most patients are diagnosed with extensive-stage (ES) SCLC with rapidly deteriorating condition.[3]
- Although most patients with ES-SCLC respond to initial therapy, responses are short-lived with the vast majority experiencing disease progression within the first year of treatment.[4]
- There is no curative treatment for SCLC that has progressed after initial treatment, and most patients receive chemotherapy for second-line therapy and beyond (2L+).[1,5]
- There is no established treatment for the third-line setting and beyond (3L+).[1,5]

OBJECTIVE

- The objective of this systematic literature review (SLR) was to evaluate clinical trial data on the efficacy and safety of 3L+ SCLC treatments, to increase understanding of the unmet need of patients with SCLC with disease progression after two lines of therapy.

METHODS

- The SLR was conducted following methodological guidance from the Centre for Reviews and Dissemination and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).
- Searches were conducted on 19 April 2022 using the OVID platform in the MEDLINE, Embase, and Cochrane Library databases. This was supplemented by hand searching to identify additional conference abstracts not indexed in the above databases.
- Two reviewers independently screened the titles and abstracts of identified citations against predefined eligibility criteria (**Table 1**), followed by full-text review of included publications.
- Data were extracted by one researcher and validated by a second researcher.
- Risk of bias assessment was performed using standardized tools (Cochrane RoB 2.0 tool and Downs and Black RoB tool).

Table 1. PICOS Eligibility Criteria

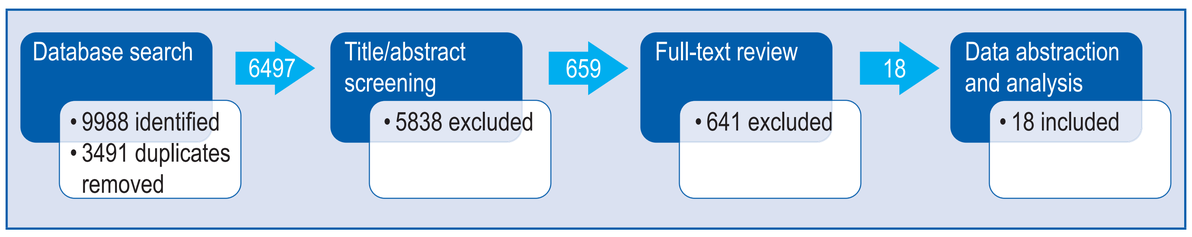
Population	Patients (≥ 18 years) with SCLC with disease progression after two lines of therapy
Intervention	Licensed by FDA/EMA, recommended by key clinical guidelines, routinely used and/or in development; BSC
Comparator	Head-to-head, BSC, placebo, or none
Outcome[a]	PFS, OS, ORR, DOR, DCR, ToT, TTD, safety, HRQoL, and utilities
Study design	RCTs and single-arm studies (phase 1b–4)
Date restriction	Full-text publications (1986[b] to April 2022), conference abstracts (2018 to April 2022)

[a] DOR, DCR, ToT, TTD, safety, HRQoL, and utilities were included in the scope of this SLR but are not reported here.
[b] The start date restriction was chosen to reflect a change in the standard of care: first topotecan clinical trial cited as part of relevant clinical guidelines in relapsed/refractory SCLC.
BSC, best supportive care; DCR, disease control rate, DOR, duration of response; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PICOS, Population, Intervention, Comparison, Outcomes and Study design; RCT, randomized controlled trial; SCLC, small cell lung cancer; SLR, systematic literature review; ToT, time on treatment; TTD, time to treatment discontinuation.

RESULTS

- Database searches returned 9988 records, of which 18 records (14 full texts and 4 conference abstracts) met the inclusion criteria and were included for data extraction (**Figure 1**).
- Supplementary searches identified no additional conference abstracts.

Figure 1. PRISMA Flow Diagram



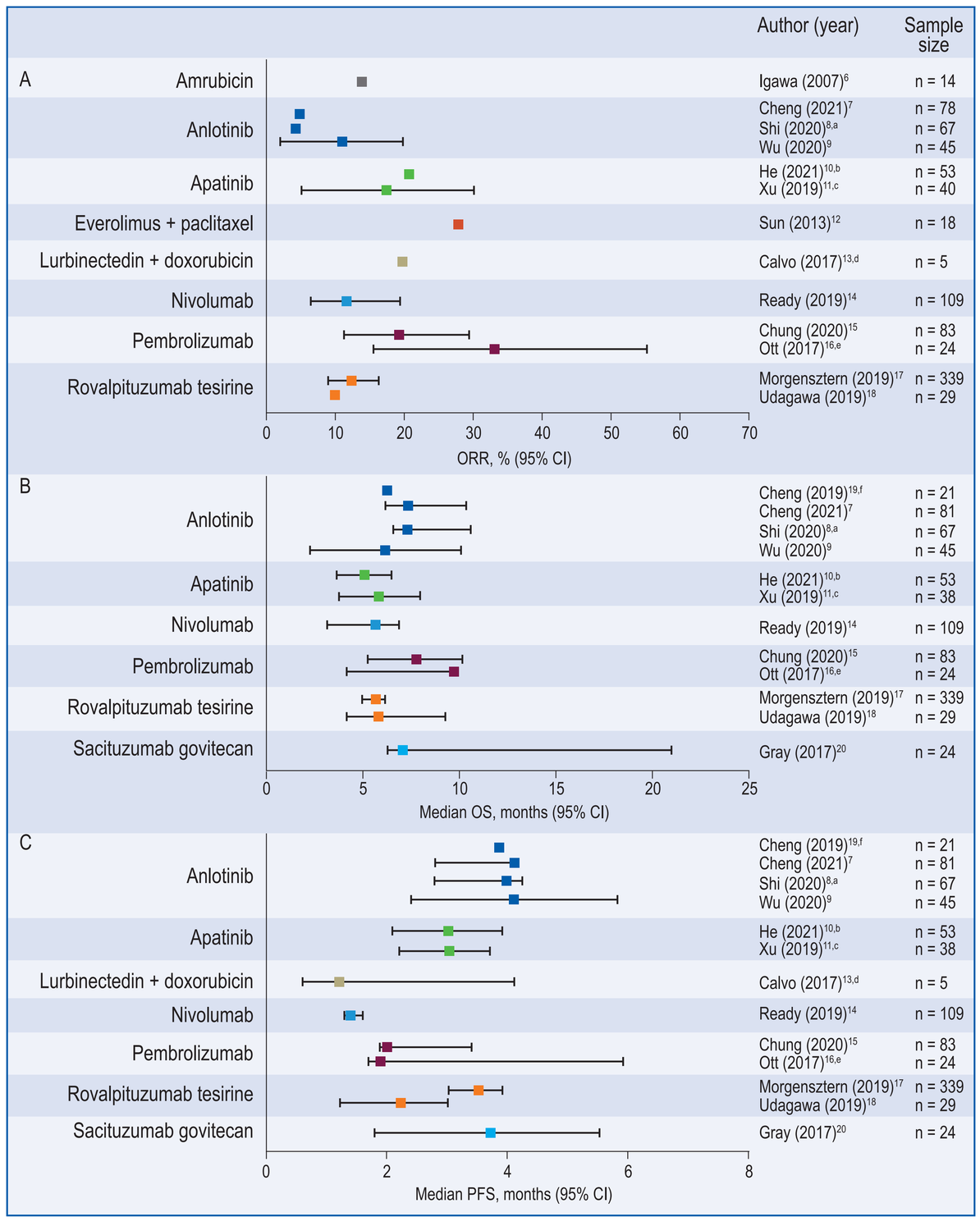
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

- The 18 publications reported data from 14 unique trials (1 double-blind, randomized controlled trial [RCT] [anlotinib vs placebo] and 13 open-label, single-arm trials) and 1 pooled analysis (including KEYNOTE-028 and KEYNOTE-158).
  - Eight of the trials were conducted in Asia (China [4], Japan [3], Korea [1]), and the remaining trials were conducted in the USA (3), and multiple countries (3); the country was not reported in 1 study.
  - The trials were phase 1 (5 trials), phase 1/2 (1), and phase 2 (7); the trial phase of 1 study was unclear. The pooled analysis combined phase 1 and phase 2 trials. None of the trials were phase 3.
- The patient populations were generally small (only 3 trials included more than 100 patients in 3L+).
- The sample sizes ranged from 6 to 339 patients.
  - Calvo *et al* (2017) included 6 patients; efficacy evaluation was based on 5 patients only.
- Among the included studies, 12 monotherapies and 4 combination therapies were investigated; none of which are recommended by the European Society for Medical Oncology treatment guidelines for recurrent SCLC (2L+).

Efficacy data

- With active treatments in 3L+, objective response rate (ORR) ranged from 4.5% to 28.0%.
- Median overall survival (OS) ranged from 5.0 to 7.7 months.
- Median progression-free survival (PFS) ranged from 1.2 to 4.1 months.
  - In the KEYNOTE-028 study, 12.5% of included patients were in the 2L setting and the reported outcomes for pembrolizumab were as follows: ORR, 33.3%; median OS, 9.7 months; median PFS, 1.9 months.
- No treatment was clearly and consistently associated with improved clinical outcomes (**Figure 2**).
- No study reported quality of life outcome data.

Figure 2. 3L+ Treatments Had Similar (A) ORR, (B) Median OS, and (C) Median PFS



[a] Subgroup of patients with refractory relapse.
[b] Apatinib + etoposide.
[c] Per protocol population.
[d] Chemotherapy-resistant disease.
[e] KEYNOTE-028, 12.5% of included patients were treated in the 2L setting.
[f] Subgroup of patients with brain metastasis.
2L, second line; 3L+, third line and beyond; CI, confidence interval; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Safety data

- Any grade adverse events (AEs) were reported for 55–100% of patients receiving active treatments.
- Overall, 9.6–63% of patients experienced AEs of grade 3 or higher.
  - The proportion of patients experiencing AEs of grade 3 or higher in the KEYNOTE-028 study was 8%.
- Reported grade 3 or higher AEs included neutropenia (5–67% of patients), thrombocytopenia (0–67%), leukopenia (0–38%), febrile neutropenia (0–21%), anaemia (0–10%), and fatigue (0–5%).

Risk of bias assessment

- According to the risk of bias assessment, the RCT identified in the SLR was of good quality with low risk of bias.
- Of the single-arm trials, 12 were scored 'fair' and 2 did not meet the criteria for assessment.

CONCLUSIONS

- Therapies in 3L+ SCLC clinical trials demonstrated limited efficacy with a high propensity for AEs.
- Given the predominantly single-arm study design, small sample sizes, and varying number of publications contributing data for each trial, the results should be interpreted with caution.
- Findings of this SLR show that no established standard of care exists in 3L+ SCLC, highlighting a significant unmet need for standardizing treatment for patients with SCLC in 3L+ setting.

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DISCLOSURES

F Dirnberger and G Suri are employees of Amgen and hold Amgen stocks. B Mayer, K Appiah, and M Rizzo are employees of Cytel, a consulting company that has provided paid consulting services to Amgen, which funded the development and conduct of this study and abstract.

ISPOR Europe 2023; Copenhagen, Denmark; 12–15 November 2023