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Clinical Outcomes in Patients With Advanced Large-Cell Neuroendocrine Carcinoma of the Lung: A Systematic Literature Review and Meta-Analysis

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Background

- Large-cell neuroendocrine carcinoma (LCNEC) of the lung, like small-cell lung cancer (SCLC), is an aggressive type of pulmonary neuroendocrine carcinoma with poor prognosis; LCNEC of the lung accounts for approximately 0.9% of all lung cancer cases¹
- Patients with advanced or metastatic LCNEC of the lung are often treated with regimens indicated for SCLC and non-small-cell lung cancer (NSCLC) due to a lack of prospective and retrospective studies specific to LCNEC of the lung²⁻⁴
- For extensive-stage SCLC, first-line (1L) chemotherapy with or without an immune checkpoint inhibitor (ICI) yields response rates of 50%–80%,^{5,6} and second-line (2L) or later chemotherapy and/or immunotherapy yields response rates of 10%–40%.^{7,8}
- To address the lack of robust data on treatment response in advanced or metastatic LCNEC of the lung, we conducted a systematic literature review and meta-analysis to summarize current evidence on clinical outcomes associated with systemic therapy in patients with advanced or metastatic LCNEC of the lung, and to quantify tumor response rates by treatment and line of therapy

Methods

Systematic literature review

- Comprehensive literature searches were conducted across Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (EMBASE), and Cochrane Central Register of Controlled Trials (CENTRAL)
 - Bibliographies of studies were cross-referenced to identify eligible studies not captured by database searches
- Study eligibility criteria were determined per prespecified PICOTS criteria (Table 1), and all publications were screened by 2 independent reviewers, with conflicts resolved by a third independent reviewer
 - Data extraction was performed by 2 independent reviewers

Table 1. Eligibility criteria (PICOTS framework)

	Inclusion Criteria
Population	Patients aged ≥18 years with advanced or metastatic LCNEC of the lung who initiated systemic anticancer therapy
Interventions	1L: any systemic anticancer therapy regimen containing ≥1 chemotherapy agent 2L or later: any systemic anticancer therapy
Comparisons	None
Outcomes	Response rate (ORR or rwRR)
Time	2000–present (sensitivity: 2016–present)
Study design	- Observational cohort studies (prospective or retrospective) - Case series - Clinical trials
Other	- English language - Sample size: 1L, n = ≥20; 2L, n = ≥15

ORR, objective response rate; rwRR, real-world response rate.

Quality assessment

- Risk of bias in included randomized trials assessed using the Cochrane Collaboration's tool⁹
- Quality of nonrandomized studies evaluated using Newcastle-Ottawa Scale (NOS)¹⁰

Meta-analysis feasibility assessment

- Meta-analysis feasibility assessment performed to
 - Identify comparable studies for pooling by grouping studies based on similarity in study design, treatments, and outcome ascertainment to determine whether quantitative synthesis is feasible
 - Assess potential sources of heterogeneity by examining participant demographics and baseline clinical characteristics to identify potential outliers; studies with methodologic flaws were noted for consideration of exclusion

Statistical analysis

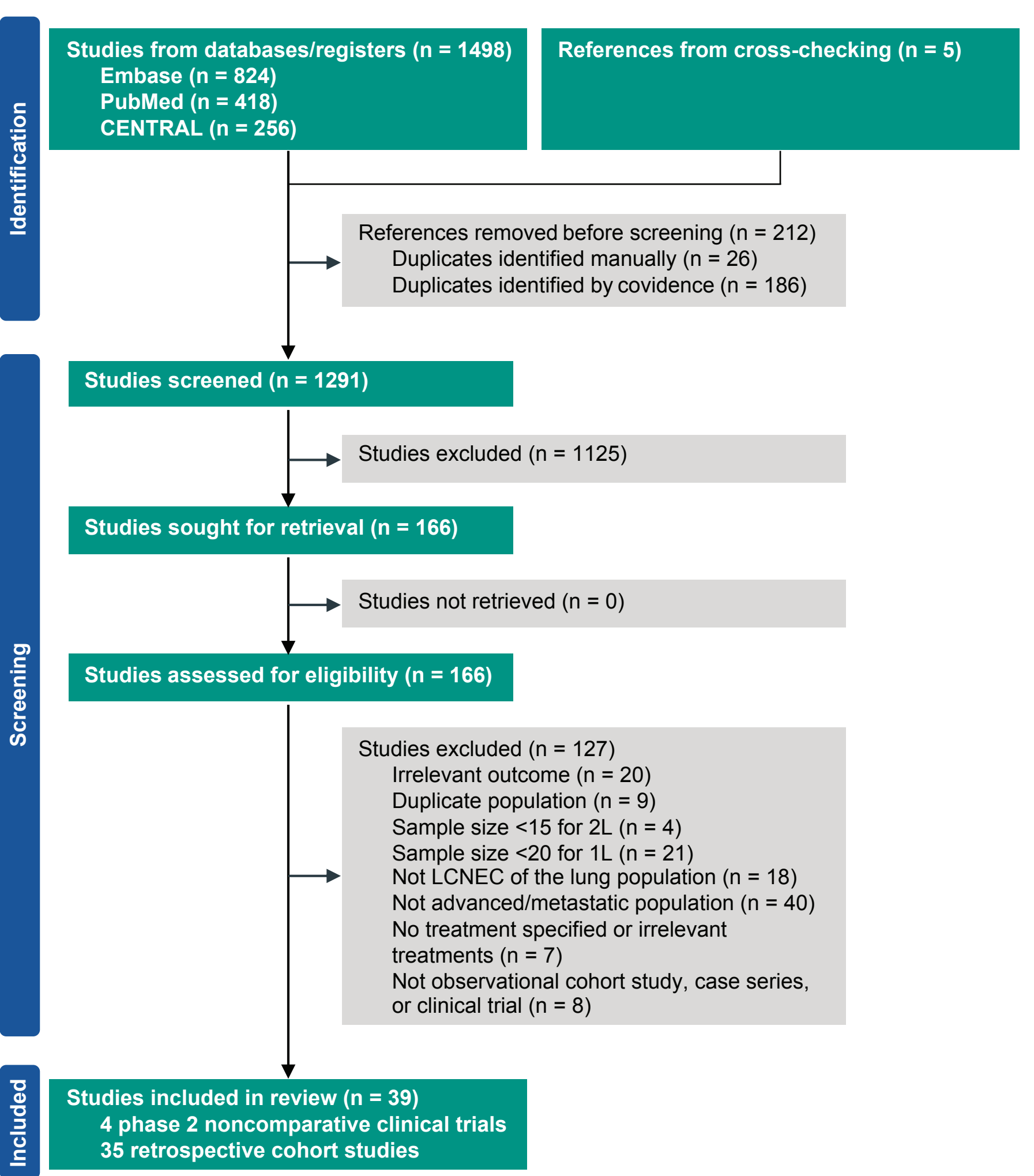
- The meta-analysis involved calculation of a pooled tumor response rate from studies that reported response (defined as the number of responders out of the total number of evaluable patients) or an overall response rate from studies that reported response as a single proportion
- Statistical heterogeneity was assessed using the Cochran's Q statistic and the I² statistic; if heterogeneity was present ($P < 0.05$), a random-effects model was employed using the meta package in R software
- Subgroup analyses based on lines of therapy and specific treatment groups were also performed

Results

Study selection

- A total of 1503 records were identified from literature searches and cross-referencing, of which 39 met eligibility criteria after screening and were included (Figure 1)

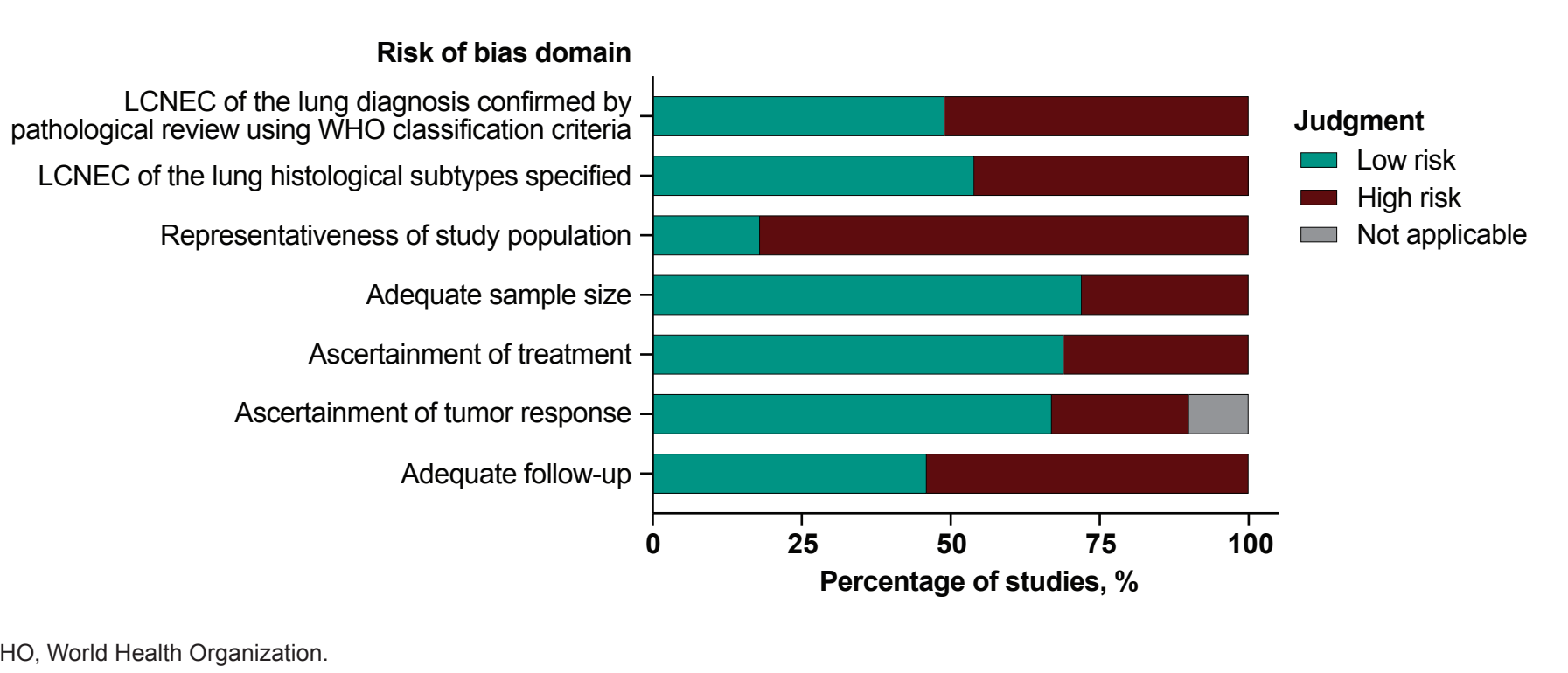
Figure 1. PRISMA flow diagram



Study quality assessment

- Most studies were of moderate quality; risk of bias domains across studies is shown in Figure 2

Figure 2. Quality assessment



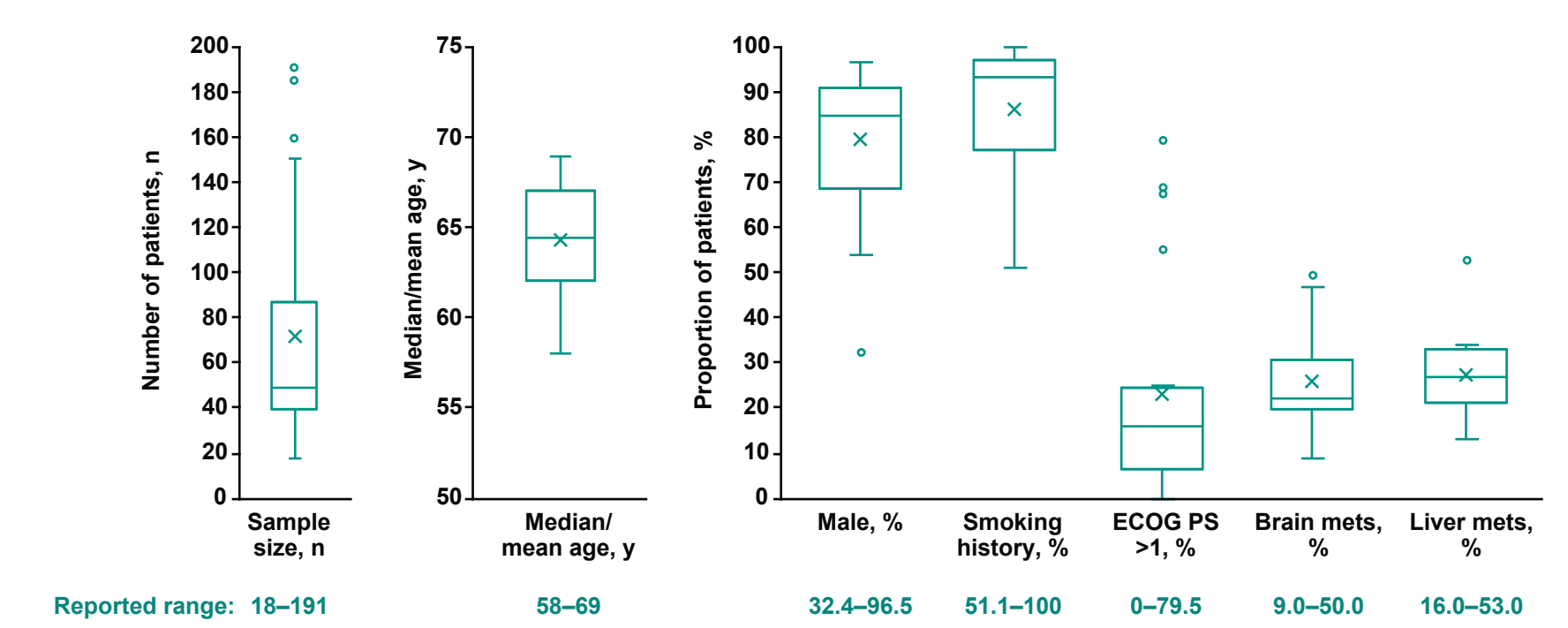
Study and patient characteristics

- The evidence base for the tumor response meta-analysis included 34 studies, with a total of 52 treatment groups and 1727 patients
 - Most studies (67.6%) included <50 patients
 - 28 studies reported 1L systemic therapy with ≥1 chemotherapy agent (clinical trials, n = 3; observational studies, n = 25), and 7 reported 2L or later systemic therapy (clinical trials, n = 1; observational studies, n = 6)
- Additional study characteristics are shown in Figure 3

References

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9. Sterne JAC, et al. *BMJ*. 2019;366:14898.
10. Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. <https://ohri.ca/en/who-we-are/core-facilities-and-platforms/ottawa-methods-centre/newcastle-ottawa-scale>.

Figure 3. Underlying study and patient characteristics



ECOG PS, Eastern Cooperative Oncology Group performance status; Mets, metastases.

Tumor response rates by line of therapy

- The pooled tumor response rate was 37.7% in patients who received 1L chemotherapy with or without ICI (Figure 4), 37.0% in those who received 1L chemotherapy only (Figure 5), and 13.1% in those who received 2L or later systemic therapy with prior platinum chemotherapy (Figure 6)
 - Response rates were generally consistent across subgroups analyzed

Figure 4. Tumor response rates of patients with advanced LCNEC of the lung receiving 1L chemotherapy with or without ICI

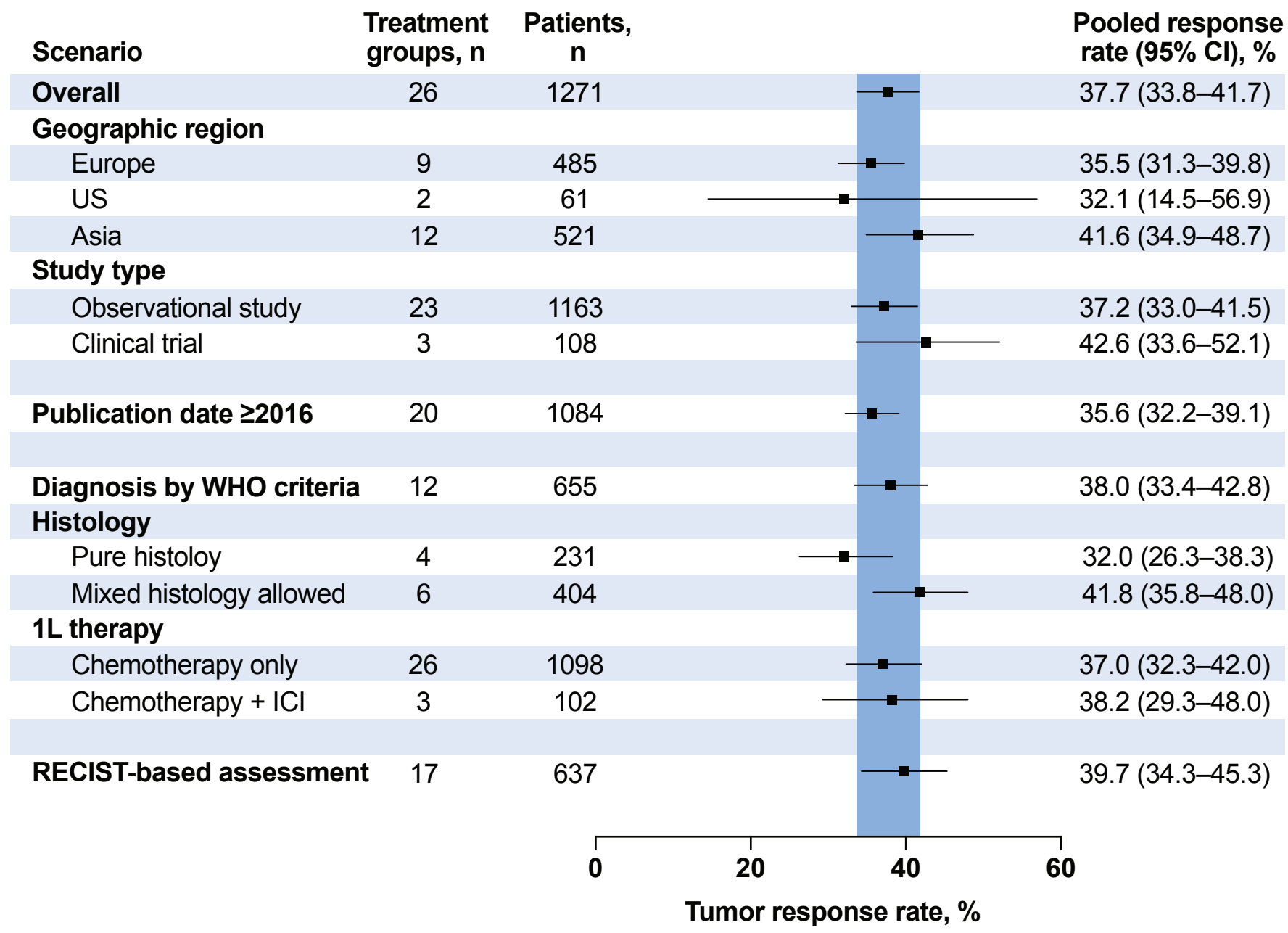
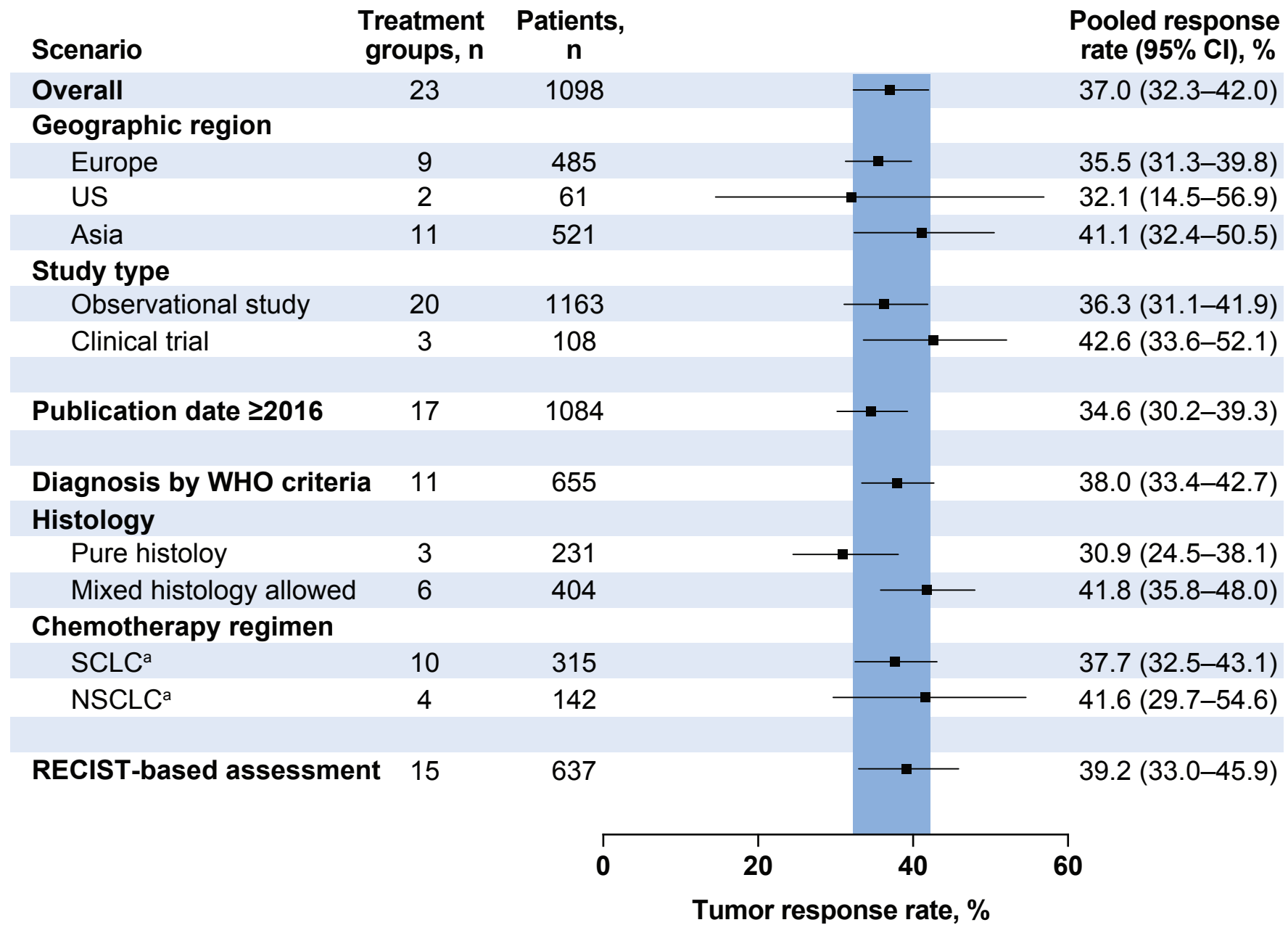
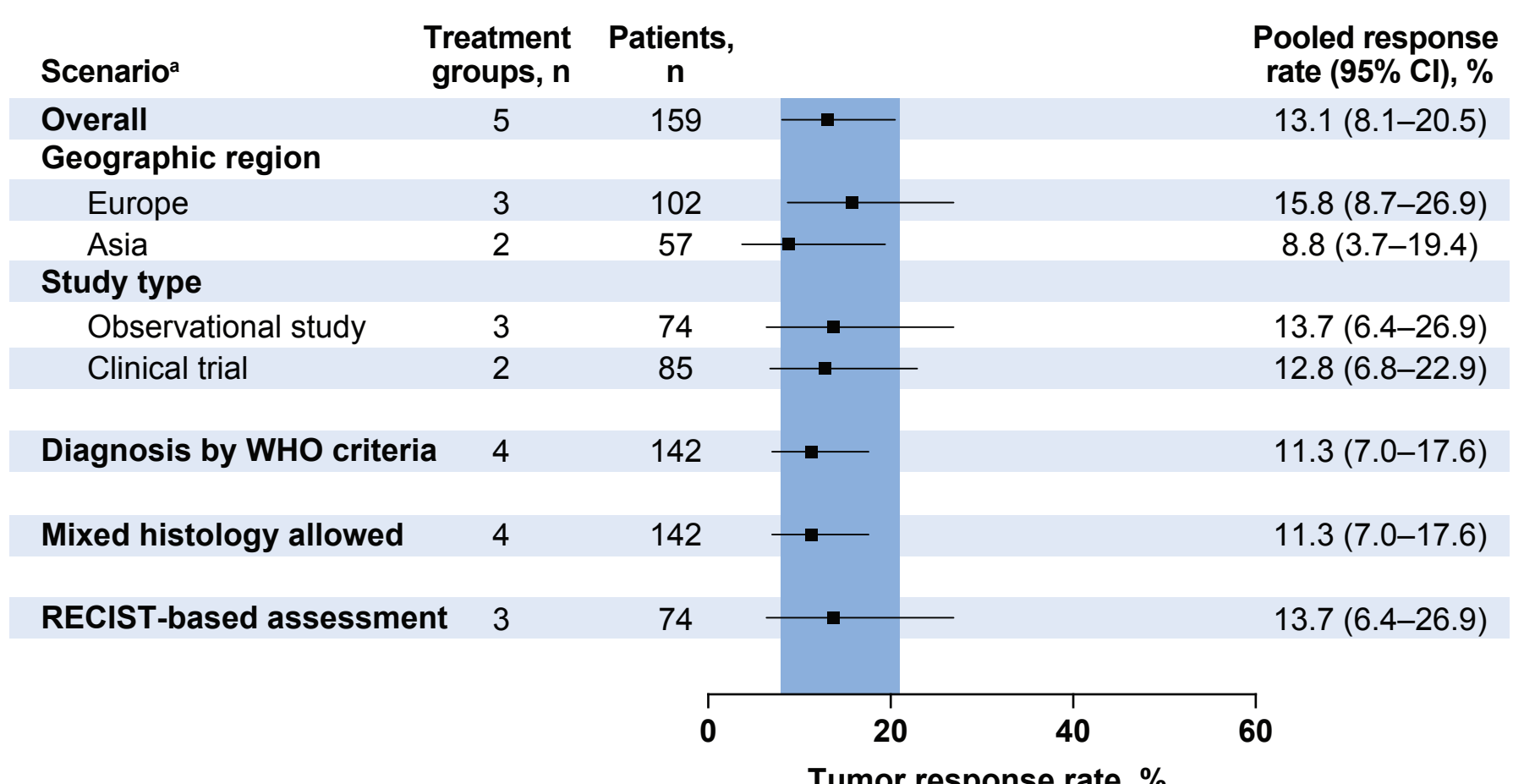


Figure 5. Tumor response rates of patients with advanced LCNEC of the lung receiving 1L chemotherapy only



*Specific chemotherapy drugs used in NSCLC and SCLC settings were not reported for all studies.

Figure 6. Tumor response rates of patients with advanced LCNEC of the lung receiving 2L/2L+ systemic therapy with prior platinum-based chemotherapy

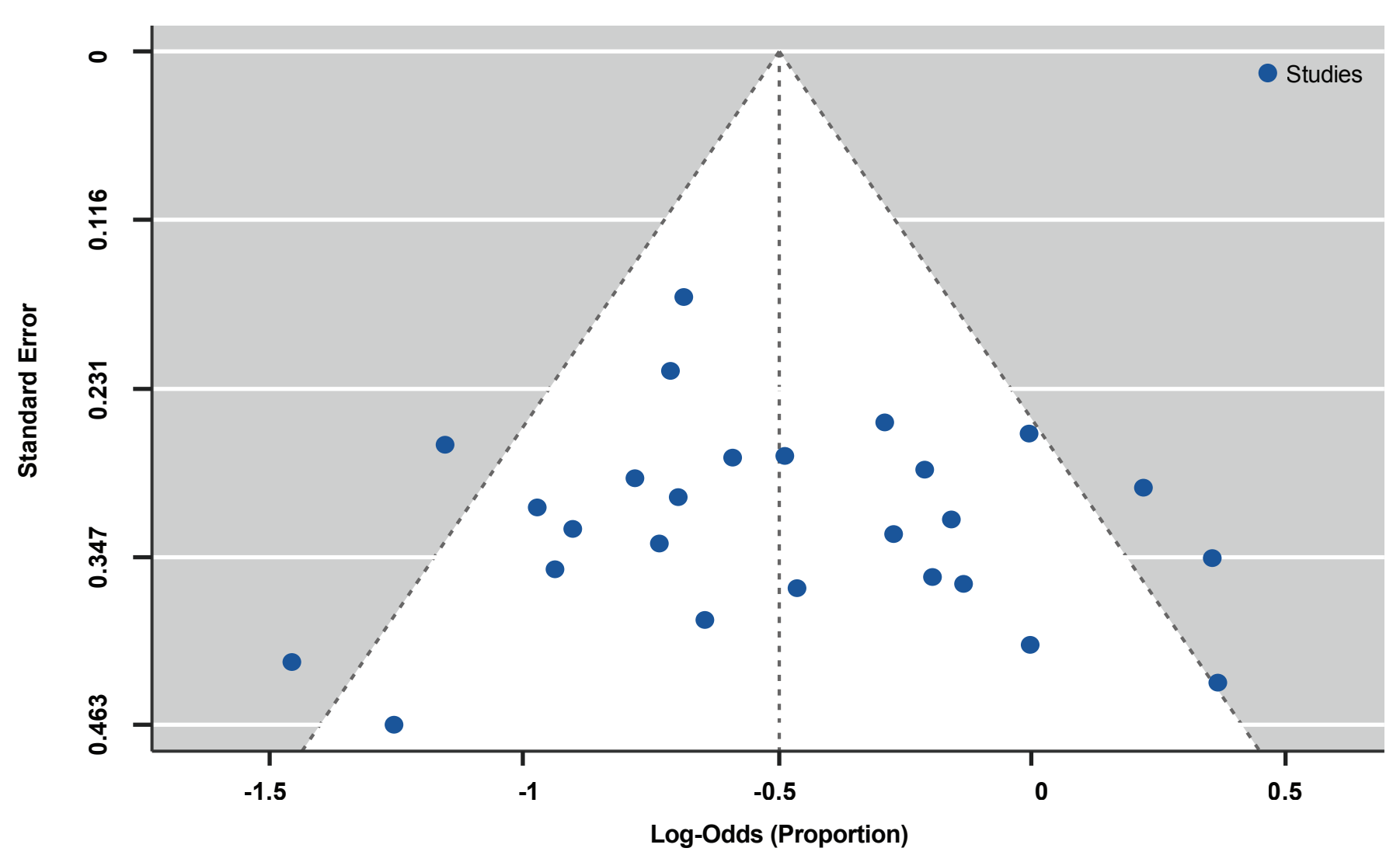


*Subgroup analyses were not conducted for studies in which the number of treatment groups was 0 or 1.

Publication bias

- No clear evidence of publication bias in studies that reported response for 1L chemotherapy with or without ICI as indicated by nonsignificant P values ($P = 0.76$ by Egger's test; $P = 0.76$ by Begg's test) and symmetry in the funnel plot (Figure 7)

Figure 7. Publication bias



Analysis limitations

- Most treatment groups had a small sample size (<100 patients), and most studies were of moderate quality
- The frequency of follow-up for tumor response likely varied in observational studies, and it is unknown whether observed tumor responses were confirmed with consecutive imaging, although most studies used RECIST-based criteria for evaluation of imaging scans
- Only a small number of studies with small sample sizes evaluated clinical outcomes in the 2L and later systemic therapy settings; thus, results have a high degree of variability and uncertainty
- Distribution of histology (mixed vs pure) was not consistently reported in the studies

Conclusions

- Pooled tumor response rates were 37.0% for 1L chemotherapy only, 37.7% for 1L chemotherapy with or without ICI, and 13.1% for 2L+ systemic therapy after prior platinum-based chemotherapy
 - Results were consistent across subgroups analyzed
- There was no clear evidence of publication bias
- Published data on treatment patterns and clinical outcomes in advanced or metastatic LCNEC of the lung are limited, and the tumor response rates shown here are lower than those reported for patients with SCLC³⁻⁸
 - These findings suggest a high unmet need for novel therapeutic strategies to improve outcomes for patients with advanced or metastatic LCNEC of the lung

Poster presented



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