

Immune-Checkpoint Inhibitors in Lung Neuroendocrine Tumors – A Systematic Review and Meta-Analysis

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Abstract: Lung neuroendocrine tumors (NETs) are well-differentiated neuroendocrine neoplasms of lung origin, including typical and atypical carcinoids (ACs). Therapeutic options for this rare disease are limited in daily clinical practice. Immune-checkpoint inhibitors (ICIs) are under clinical investigation. Here, we report a systematic reappraisal about ICIs results in lung NETs. We reviewed articles on observational or interventional studies that reported efficacy data of ICIs in lung NETs. Case reports and studies with insufficient data were excluded from the analysis. We searched the electronic databases Medline, Embase, Web of Science, and Cochrane Library up to May 2024. Two investigators independently screened the identified records and assessed studies quality. We summarized the results descriptively and in a meta-analysis of ORR according to the type of intervention. The search retrieved 1344 records. After selection, we included 11 studies in the meta-analysis of ORR, with a total of 128 adult patients with lung NET (25% ACs) that were progressing after at least one line of systemic therapy, including treatment with somatostatin analogs. Ten studies were Phase II, and 1 study was phase Ib. The summary ORR was 14.7% (95% CI, 5.8–32.2), 44.4% (27.2–63.1) for ACs. Subgroup analysis by intervention types showed a trend for lower ORR of lung NETs treated with ICI monotherapy (ORR: 2.7%; 0.0–63.7) compared with combinations (p-value: 0.056). The combination of temozolomide plus nivolumab showed the highest ORR (66.7%; 33.3–88.9). The median OS (reported in 2 studies) was not reached. Safety was consistent with historical data of ICIs. Our work suggests that ICIs are a promising treatment for patients with lung NETs, especially ACs, and warrant further investigation in more focused studies.

Keywords: immunotherapy, immune-checkpoint inhibitors, neuroendocrine tumor, carcinoid tumor, pulmonary

Introduction

Lung neuroendocrine tumors (NETs) are well-differentiated epithelial neuroendocrine neoplasms (NENs) arising in the lung, which correspond to 30% of all NETs. These comprise typical carcinoids (TCs) and atypical carcinoids (ACs), regarded as low- and intermediate-grade NETs, respectively (Table 1).^{1,2} Although they are rare and relatively indolent, their prevalence has significantly increased in the past decades and distant metastases may occur, as in up to 30% of ACs.^{3–7}

Treating advanced lung NETs is notoriously difficult. Treatment approaches differ depending on disease features (such as histological grade, tumor burden, growth rate, hormone-related symptoms, somatostatin receptors uptake level), patient's characteristics (such as performance status, age, comorbidities and preferences), and local accessibility and experience.^{8,9} The treatment goal in this setting is to control tumor growth and hormone-related symptoms. Individual therapeutic options must be discussed at a multidisciplinary tumor board in a reference center, and patients should be

Table 1 Lung Neuroendocrine Neoplasms Classification

Well-differentiated neuroendocrine neoplasms = Neuroendocrine <i>tumors</i> or carcinoids	Typical carcinoid (or G1 NET)	>5 mm carcinoid tumors and <2 mitoses/2mm ² , lacking necrosis
	Atypical carcinoid (or G2 NET)	Carcinoid tumors with 2–10 mitoses/2mm ² and/or focal necrosis
Poorly-differentiated neuroendocrine neoplasms = Neuroendocrine <i>carcinomas</i>	Small cell lung carcinoma	>10 mitoses/2mm ² and small cell morphology
	Large cell neuroendocrine carcinoma	>10 mitoses/2mm ² and large cell morphology

Abbreviation: NET, neuroendocrine tumor.

referred for clinical trials, when available. Watchful waiting may be considered in asymptomatic patients with low tumor burden. Surgery and other locoregional or ablative therapies may be considered throughout the course of disease. Somatostatin analogs (SSAs), lanreotide or octreotide, should be prescribed for all patients with functioning tumors for carcinoid syndrome control, and they are also recommended as first-line antiproliferative treatment for advanced lung NETs, particularly if low grade and positive somatostatin receptor imaging.^{10–12} Everolimus is the only other anti-tumor therapy approved in non-functioning advanced lung NETs.^{13–15}

Chemotherapy (ChT, eg temozolomide ± capecitabine) can also be used considering its efficacy and safety profile.^{16–18} Peptide receptor radionuclide therapy (PRRT) with lutetium (177Lu-DOTATATE) is a promising therapy¹⁹ that can currently be offered only within clinical trials (eg NCT05918302²⁰).

Immune evasion by tumors plays a crucial role in tumorigenesis and progression.

Compared to other lung cancers, the immunobiology of lung NETs is poorly described, but a small series of TCs showed its microenvironment to be less inflammatory.²¹ Over the past few years, immunotherapy with immune-checkpoint inhibitors (ICIs), such as anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), anti-programmed cell death protein-1 (PD-1) and/or its ligand (PD-L1) monoclonal antibodies, has been investigated for the treatment of NETs^{22–43} and has been addressed in different comprehensive reviews.^{44–47}

Here, we try to answer the unmet need of evidence-based treatment options for patients with advanced or progressive lung NETs. We first report a systematic review about ICIs in this population and present summary measures of objective response rate (ORR) of different interventions with ICIs (as monotherapy, dual therapy or in association with other cancer therapies).

Objectives

We aim to assess the efficacy of ICIs in adult patients with advanced or progressive lung NETs, by performing a systematic review of the evidence about this topic and performing a meta-analysis of the objective response rate (ORR).

Materials and Methods

Search Strategy and Data Sources

Three study investigators (RP, LB, LG) and an experienced medical librarian designed and conducted a comprehensive literature search that led to this systematic review and meta-analysis. We searched the electronic databases MEDLINE, Embase, Web of Science, and Cochrane Library. Various combinations of database-specific controlled vocabulary (subject headings) were used, supplemented by keywords, title and abstract terms for the concepts and synonyms relating to lung carcinoid tumors and ICI. Bibliographies of relevant papers were examined, and citing articles were identified using ISI Web of Science. No language and date restrictions were applied. Details regarding keywords and full search strategy are presented separately in [supplementary data](#). Searching was further complemented with trials registered on clinicaltrials.gov, conference abstracts and review articles references, from the latest years. After removal of record duplicates, two investigators (RP, LB) performed a blind screening of the eligible papers by examination of abstracts and titles. Doubts or incoherences were resolved by a third investigator (LG). If a paper was deemed relevant,

the full-text version was obtained and reviewed, applying the appropriate inclusion and exclusion criteria. The search protocol for this review was not registered. The search was performed up to May 2024.

Selection Criteria

We selected articles related to observational or interventional studies evaluating and reporting efficacy and/or safety data of ICIs in adult patients with advanced lung NETs. These criteria were defined according to PICOS approach (Table 2). Case reports were excluded from the review. The studies that included only 1 lung NET patient or with insufficient data were excluded from the meta-analysis but might be commented on the qualitative synthesis.

Data Extraction

The following information from the published papers were extracted and coded: digital object identifier (DOI) of the record, *Clinicaltrials* ID of the study, authors, year of publication, title, study design, population, intervention/drugs, type of intervention, number of previous therapies, number of lung NETs (and specifically ACs) and their ORR [defined as the percentage of lung NETs that had partial response (PR) or complete response (CR) as best response], duration of follow-up, progression free survival (PFS), overall survival (OS) or disease control rate [defined as the percentage of either PR, CR or stable disease (SD)].

Statistical Methods

We used generalized linear mixed models to calculate summary ORR for the lung NETs, and specifically ACs, considering distinct types of intervention. These included ICI monotherapy, dual ICI, combination of chemotherapy with ICI, and combination of tyrosine kinase inhibitor (TKI) with ICI.

Summary ORR was obtained with the Maximum Likelihood estimator.

Homogeneity of effects across studies were quantified by I^2 , which represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance.

Meta-regressions and subgroup analyses were conducted to quantify between-study heterogeneity among studies, by looking if the type of intervention could influence the estimates.

All the statistical analyses were performed using R software (<http://www.r-project.org>) version 4.4.1 throughout the packages “metafor”.

Results

Study Selection and Data Extraction

The search identified 1344 records, from which we selected 11 articles published between 2020 and 2024, included in the present meta-analysis^{22–32} (Figure 1). Three additional articles were included in the qualitative analysis, being excluded

Table 2 PICOS Approach for Defining Eligibility Criteria

	Description
Population/ Disease	Adult patients of all genders with advanced well-differentiated lung neuroendocrine neoplasm (typical carcinoid, atypical carcinoid, non-otherwise specified carcinoid or neuroendocrine tumor G1-G3)
Intervention/ Treatment	Immunotherapy, with ICI, single or combined therapy (single agent ICI, double agents ICI, ICI combined with another drug)
Comparison	(ICI monotherapy vs combined therapies; historical comparators).
Outcomes	Treatment response (objective response rate).
Study design	Interventional or observational (prospective or retrospective cohort) studies

Abbreviations: ICI, immune checkpoint inhibitor; G, grade.

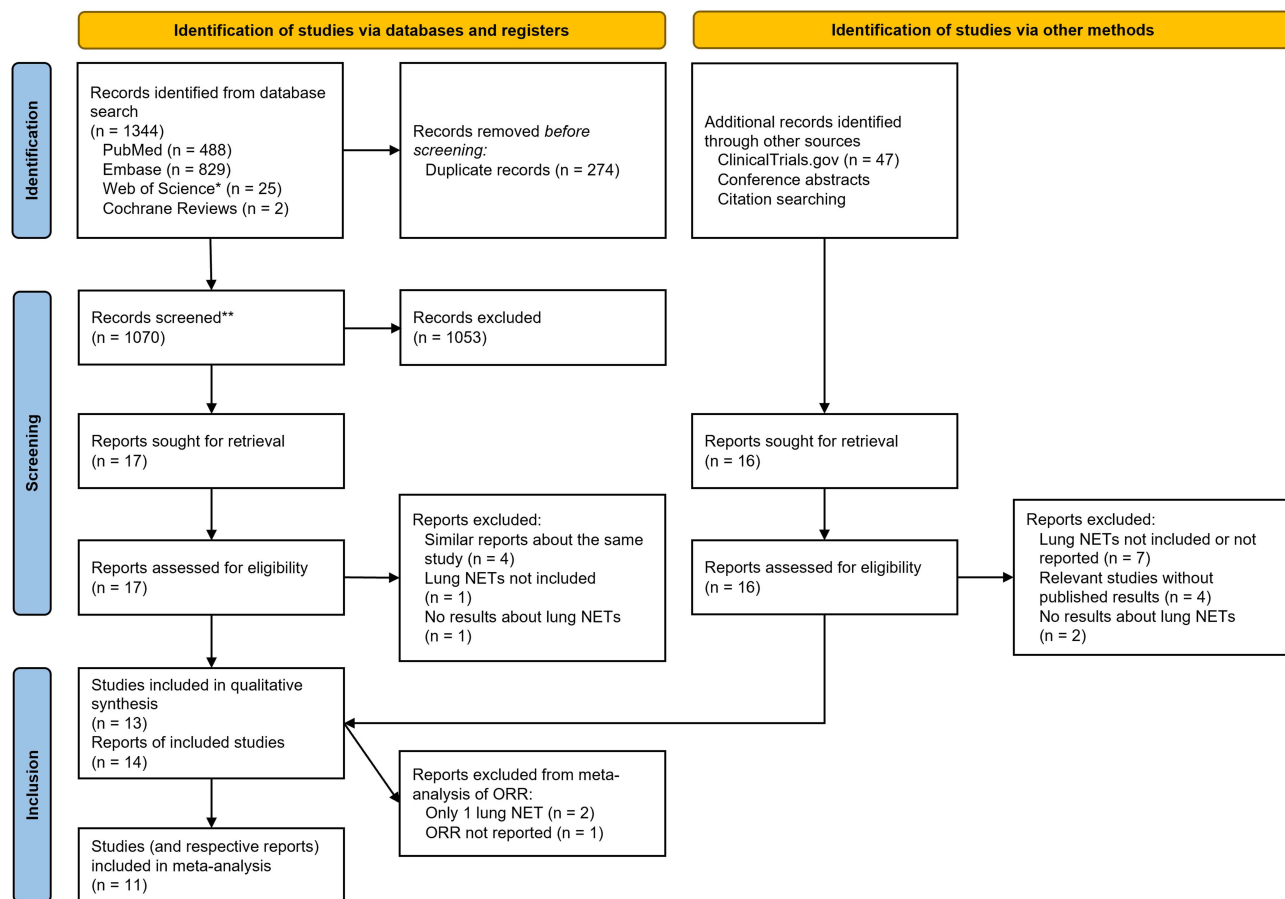


Figure 1 Flowchart of studies selection. *Filter: Highly cited papers; **The authors RP and LB independently screened the title and abstract of the identified records using the tool Rayyan for systematic reviews, available at new.rayyan.ai. Adapted from: Page MJ, McKenzie J E, Bossuyt P M et al, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; 372:n71. Available at www.prisma-statement.org/prisma-2020-flow-diagram Creative Commons.

Abbreviations: NET, neuroendocrine tumor; ORR, Objective response rate.

from meta-analysis because they included only 1 lung NET participant each or did not specify the exact number of lung NET participants.^{33–35}

Study Characteristics

The characteristics of the 11 studies (and respective record) included in the final analysis are shown in [Table 3](#). The quality assessment table of these studies is available in [Supplementary Table 1](#). Overall, these studies included 128 lung NETs, 32 of them were ACs. Ten studies were phase II and 1 was phase Ib. All patients were pretreated with at least one line of therapy.

Effects of ICIs on Lung NETs

Meta-Analysis of ORR

In the overall analysis ([Figure 2](#)), based on 11 studies,^{22–32} the summary ORR of lung NETs was 14.7% (95% CI 5.8–32.2).

Subgroup analysis of intervention types showed a lower ORR for lung NETs treated with ICI monotherapy (ORR: 2.7%; 95% CI 0.0–63.7), compared to dual ICI (ORR: 24.5%; 95% CI 11.8–44.1) or ICI combined with other therapies (ORR: 18.7%; 95% CI 1.6–76.2) with $I^2 = 54.96\%$ ([Figure 3](#)). The meta-regression analysis by intervention type suggested that there was insufficient evidence to conclude that there were statistically significant differences between these groups (p-value = 0.164). However, we observed a borderline significant difference when comparing ICI monotherapy with dual/combination strategies (p-value = 0.056) in favor of the latest.

Table 3 Characteristics of the Studies Included in the Meta-Analysis

Ref.	DOI	Clinicaltrials.gov ID	Population/Cohort	Lung NETs, n	Intervention/ Drugs	Type of Intervention	Study Design
Al-Toubah 2024 ²²	10.1016/j.esmoop.2024.102386	NCT03290079	Advanced non-pancreatic NET (n=20)	5	Pembrolizumab + lenvatinib	TKI+ICI	Phase II
Capdevila 2023 ²³	10.1038/s41467-023-38611-5	NCT03095274	Advanced NENs, typical/atypical lung NET cohort (n=27)	27	Durvalumab + tremelimumab	Dual ICI	Phase II
Capdevila 2023 ²⁴	10.1016/j.annonc.2023.09.670	NCT04400474	Advanced and refractory endocrine tumors (n=93), lung NET cohort (n=9)	9	Cabozantinib + atezolizumab	TKI+ICI	Phase II
Chan 2022 ²⁵	10.1016/j.jejc.2022.03.029	NCT03278379	NET-002: Advanced G2-3 GEP NET or bronchial AC (n=17)	5	Avelumab	ICI	Phase II
Klein 2020 ²⁶	10.1158/1078-0432.CCR-20-0621	NCT02923934	Advanced NETs (n=29)	10	Nivolumab + ipilimumab	Dual ICI	Phase II
Mehnert 2020 ²⁷	10.1002/cncr.32883	NCT02054806	PD-L1 positive carcinoid tumors cohort (n=25)	9	Pembrolizumab	ICI	Phase Ib
Owen 2023 ²⁸	10.1158/1078-0432.CCR-22-1552	NCT03728361	Advanced NETs (n=28)	9	Nivolumab + temozolomide	ChT+ICI	Phase II
Patel 2020 ²⁹	10.1158/1078-0432.CCR-19-3356	NCT02834013	Nonpancreatic neuroendocrine NENs cohort (n=32)	6	Nivolumab + ipilimumab	Dual ICI	Phase II
Scott 2021 ³⁰	10.1200/JCO.2021.39.15_suppl.e16201	NCT03420521	Nonfunctional NET of lung, pancreas, or GI origin (n=9)	6	Nivolumab + ipilimumab	Dual ICI	Phase II
Strosberg 2020 ³¹	10.1158/1078-0432.CCR-19-3014	NCT02628067	Advanced NET (n=107)	14	Pembrolizumab	ICI	Phase II
Yao 2021 ³²	10.1530/ERC-20-0382	NCT02955069	Advanced NET (n=95), thoracic cohort (n=30)	28	Spartalizumab	ICI	Phase II

Note: Lung (or thoracic) NET cohorts are highlighted in bold.

Abbreviations: AC, atypical carcinoid; ChT, chemotherapy; CTLA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune-checkpoint inhibitor; NET, neuroendocrine tumor; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SSA, somatostatin analog; TC, typical carcinoid; TKI, tyrosine kinase inhibitor; GEP, gastroenteropancreatic; GI, gastrointestinal; NEN, neuroendocrine neoplasm.

The summary ORR of ACs (Figure 4), based on 4 studies,^{23,28,30,33} was 44.4% (95% CI 27.2–63.1).

We did not find any indications for a potential publication bias for any of the analyses.

Qualitative Analysis of Other Data

The trials of spartalizumab (anti-PD-1) in advanced solid tumors (N=58) and nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA-4) in high-grade NENs (N=19) were excluded from the meta-analysis because they included only 1 lung NET patient each; notably, these 2 patients had an AC and achieved a PR.^{26,32} The multicohort trial of atezolizumab (anti-PD-1) was excluded from the meta-analysis because the authors did not specify the exact number of lung NETs (range 1–4); they reported 0% ORR and 100% SD and clinical benefit in the NETs cohort.³⁵ The trial of atezolizumab plus bevacizumab in advanced and progressive NETs included 5 (20%) lung NETs, but was excluded because the authors did not report the outcomes of that subgroup of patients.³⁷

We could not perform a meta-analysis of other outcomes, such as OS, PFS or other disease control measures, because of insufficient or heterogeneous reported data.

The median OS (mOS) of lung NETs, reported in 2 studies, was not reached (NR). These specifically evaluated the combinations of durvalumab plus tremelimumab (range: 0.3–41.3 months; 12 months-OS: 70.4%), and nivolumab plus temozolomide (95% CI: 8.8 months-NR; 12 months-OS: 81.8%).^{23,25,28}

The median PFS (mPFS) of lung NETs was reported in 2 studies:^{23,24} 8.4 months (7.7 - NR) for cabozantinib plus atezolizumab, and 5.6 months (4.9–6.2) for durvalumab plus tremelimumab. Additionally, a NR mOS and a mPFS of 3.5

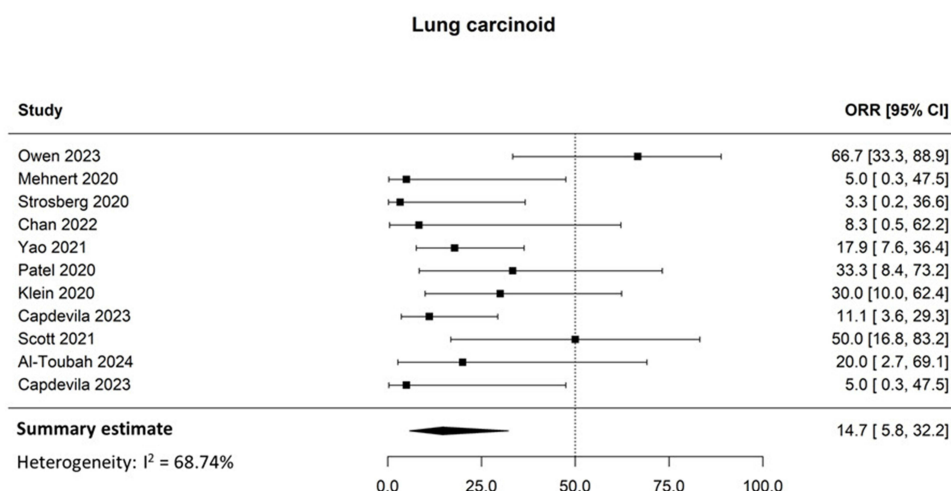


Figure 2 Forest plot of study-specific and summary objective response rate of lung neuroendocrine tumors (lung carcinoid).^{22–32}

Abbreviations: ChT, chemotherapy; ICI, immune-checkpoint inhibitor; ORR, Objective response rate; TKI, tyrosine kinase inhibitor.

months was reported for lung “NEN” patients treated with avelumab monotherapy, including 1 (16.6%) patient with small cell lung cancer (SCLC),²⁵ and a mPFS of 11.1 months (3.0–29.0) was reported for lung “NEN” patients treated with nivolumab plus temozolomide, including 1 (9.1%) patient with “lung neuroendocrine carcinoma” and 1 (9.1%) with unknown histology.²⁸

The other studies did not report survival outcomes of patients with lung NET.

Regarding disease control measures, durvalumab (anti-PD-L1) plus tremelimumab (anti-CTLA-4) yielded a “clinical benefit rate”, defined as the percentage of patients achieving PR/CR or SD at 9 months, of 66.7% (95% CI 47.9–82.1) in lung NENs.²³

No safety concerns were raised of these therapies for the lung carcinoid population.

Four additional trials assessing the combination of ICIs with different TKI (cabozantinib and lenvatinib) and with PRRT were ongoing, without published results, at the time of the review. Main characteristics of these trials are summarized in [Supplementary Table 2](#).

Discussion and Conclusion

This systematic review and meta-analysis highlights that, despite the growing interest in ICIs for NENs, no trial to date has been specifically designed to evaluate ICI therapy in [well-differentiated] lung NETs and few trials had pre-planned lung (or thoracic) NET cohorts.^{23,24,32} Most evidence derives from small subgroups within broader basket or phase II trials, often with significant heterogeneity in design, therapeutic regimens, and endpoints. Moreover, the design of some trials could have precluded the benefit for lung NET patients. For instance, the trial of pembrolizumab plus lenvatinib for non-pancreatic NETs was stopped earlier because of limited antitumor activity (ORR of 10%). While, if we consider only primary lung location, the ORR threshold to proceed with the trial would have been achieved.²¹ Furthermore, in the spartalizumab trial, the study was negative due to the unmet goal of the primary endpoint that was 10% ORR in the overall population, while ORR was 17.9% in the lung NET cohort.³¹ This supports the notion that lung NETs are distinct entities from NETs arising in other sites, rather than a single, homogeneous disease.⁴⁸ All of this makes it difficult to interpret data and to draw practice-changing conclusions.

When comparing treatment strategies (ie, types of intervention), our findings suggest that ICI monotherapy demonstrates limited activity in lung NETs, with a pooled ORR of 2.7%. However, this limited efficacy should be interpreted with caution, as tumor growth control—rather than objective response—may still represent a meaningful therapeutic goal in advanced lung NETs. Future studies should prioritize survival endpoints. In contrast, combinatorial approaches, particularly dual ICI regimens or ICIs combined with other therapies (eg, temozolomide or tyrosine kinase inhibitors), are associated with higher ORRs—24.5% and 18.7%, respectively. Notably, the combination of nivolumab plus

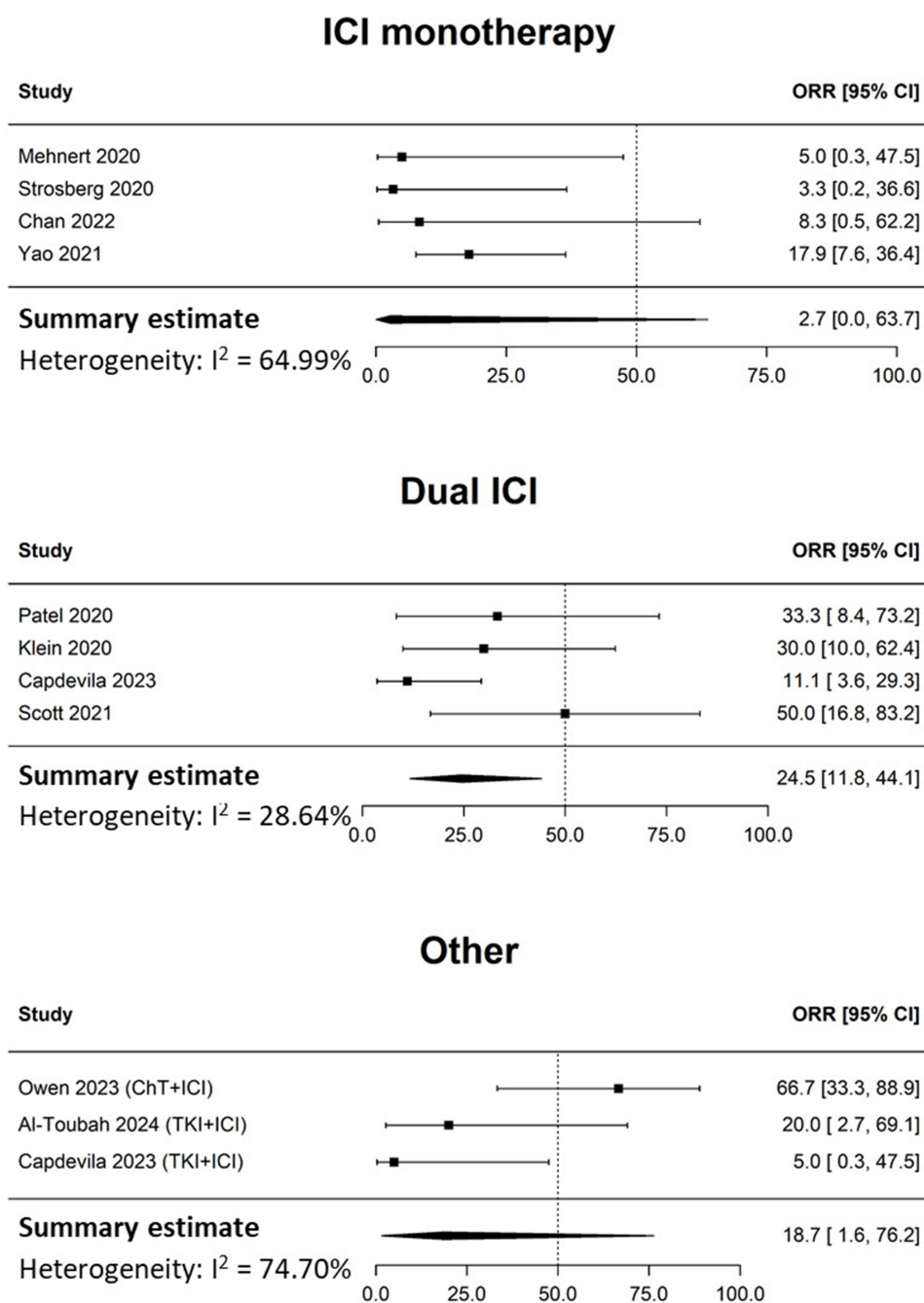


Figure 3 Forest plot of study-specific and summary objective response rate of lung neuroendocrine tumors (lung carcinoids) by type of intervention - in ICI monotherapy,^{25,27,31,32} dual ICI^{23,26,29,30} and others (TKI+ICI, ChT+ICI combined).^{22,24,28}

Abbreviations: ChT, chemotherapy; ICI, immune-checkpoint inhibitor; ORR, Objective response rate; TKI, tyrosine kinase inhibitor.

temozolomide yielded the highest ORR (66.7%) and a promising mPFS of 11.1 months, which is relatively better than the historical controls of other currently available therapies recently reviewed elsewhere.^{44,49} Although it is difficult to understand the different contributions of chemotherapy and ICI to these results, it seems that they are synergistic to some extent, and this could be considered especially when tumor shrinkage is needed. While statistical significance was not reached, a borderline difference ($p = 0.056$) supports the superiority of combination therapies over monotherapy and warrants further evaluation in controlled settings.

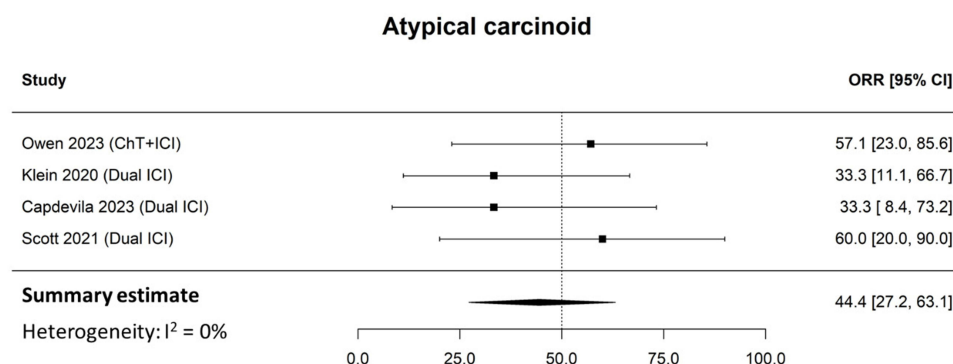


Figure 4 Forest plot of study-specific and summary objective response rate of atypical carcinoids.^{23,26,28,30}

Abbreviations: ChT, chemotherapy; ICI, immune-checkpoint inhibitor; ORR, Objective response rate.

Regarding histological subtypes, while ICIs are part of the standard treatment of poorly differentiated NENs such as extensive-stage SCLC^{50–52} and advanced Merkel cell carcinoma, their role in well differentiated NENs, particularly in lung NETs, is still not established.^{53–55} Our subgroup analysis indicates that ACs appear to derive greater benefit from ICI therapy than TCs. The summary ORR in studies that reported outcomes by subtype was 44.4% for ACs—substantially higher than the overall population. This aligns with prior observations that ACs, due to their higher proliferative activity and possibly greater mutational burden, may be more immunologically responsive. These findings underscore the need for future trials to stratify outcomes by histological subtype and investigate tailored immunotherapy strategies.

Some strengths of this review are its proper and solid methodology and accurate search method. Also, by retrieving specific results about lung NETs patients included in large basket trials of ICIs or in trials with NENs of different primary sites, we were able to perform a meta-analysis of ORR of ICIs in lung NETs, partially overcoming the limitations of poorness of evidence and high heterogeneity of previous studies.

Clinical implications of our findings suggest that while ICIs cannot yet be considered standard care in lung NETs, particularly as monotherapy, they may represent a promising option when used in combination, especially for ACs or in the setting of disease requiring rapid tumor shrinkage. The lack of robust survival data and biomarker-driven analyses limits definitive conclusions but highlights the unmet need in this field.

In conclusion, our review provides the first pooled estimate of ICI activity specifically in lung NETs, partially overcoming the limitations of fragmented and heterogeneous literature. While the evidence remains preliminary, it suggests a role for combination immunotherapy and histology-driven approaches, particularly for ACs. Prospective, lung NET-focused trials are urgently needed to validate these findings, optimize patient selection, and define the place of ICIs in the therapeutic landscape of this rare tumor type.

Data Sharing Statement

Data supporting the results reported in the manuscript may be requested from the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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