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Original Article

5-Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan as a Potential Standard for Second-line Therapy in Extrapulmonary Neuroendocrine Carcinomas

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Abstract

Background: Neuroendocrine carcinomas (NECs) are classified by the World Health Organization as poorly differentiated, aggressive Grade 3 tumors with high proliferative indices and frequent lung involvement. While initial treatment for advanced NEC typically involves etoposide and platinum-based therapies, standardized options for subsequent lines of treatment are lacking. This study evaluates the efficacy and outcomes of various second-line treatments for NECs following progression after initial therapy. **Materials and Methods:** A retrospective cohort study was conducted at Taipei Veterans General Hospital, Taiwan, from January 2016 to June 2023. The study included patients aged 18 years or older diagnosed with extrapulmonary NEC who had progressed following initial platinum and etoposide therapy. Treatment response and survival outcomes were assessed. **Results:** The study analyzed 34 patients across four treatment regimens: 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI), 5-fluorouracil, leucovorin, and irinotecan, 5-fluorouracil, leucovorin, and Nivolumab + Ipilimumab. The FOLFOXIRI regimen demonstrated the highest objective response rate of 33.3% and a disease control rate of 66.7%, compared to the other groups, with a median progression-free survival of 4.1 months and median overall survival of 9.7 months. **Conclusion:** The FOLFOXIRI regimen shows potential as an effective second-line treatment for patients with extrapulmonary NEC who have progressed after first-line therapy with platinum/etoposide.

Keywords: Extrapulmonary, 5-fluorouracil, leucovorin, and irinotecan, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan, second-line therapy, ipilimumab, neuroendocrine carcinoma, 5-fluorouracil, leucovorin, neuroendocrine carcinomas, nivolumab

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Introduction

Classification and characteristics of neuroendocrine neoplasms

In 2022, the World Health Organization classified neuroendocrine neoplasms (NENs) into two groups, well-differentiated tumors and poorly differentiated carcinomas based on morphological characteristics and proliferation markers such as the Ki-67 index.[1] Neuroendocrine carcinomas (NECs) are defined as poorly differentiated, aggressive Grade 3 (G3) NENs. These carcinomas display pronounced nuclear and cellular atypia, severe nuclear molding, and preserved neuroendocrine markers. The Ki-67 proliferation index for NECs typically starts at 20% and often exceeds 50%.[2] Lung NECs are the most frequently occurring subtype of poorly differentiated NECs, accounting for 91.3% of cases, and they have been extensively studied. In contrast, extrapulmonary NECs are rare.[3] Due to the lack of prospectively collected data, the treatment guidelines for extrapulmonary NECs are mainly based on expert opinion and adaptations from management strategies for lung small-cell carcinoma.[4,5]

Challenges in second-line therapies

First-line chemotherapy for advanced NECs typically involves a combination of etoposide and platinum-based agents,[4,5] and the response rate in the largest reported cohort was 31%.[6] However, there is currently no established standard regimen for treatment beyond first-line therapy.[4,5] Various studies have explored alternative treatment options for patients with disease progression following platinum-based therapy. A retrospective study of progressive NEC patients receiving various second-line therapies, including irinotecan, paclitaxel, temozolomide, and topotecan, after first-line platinum/etoposide treatment demonstrated limited efficacy and short survival.[7] The median progression-free survival (PFS) was 2.3 months, and the median overall survival (OS) was 6.2 months, with no regimen demonstrating superiority over others.

The phase II PRODIGE 41-BEVANEC trial compared 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) with or without bevacizumab.[8] This trial did not demonstrate a benefit from adding bevacizumab to the chemotherapy regimen but did report a 6-month OS rate of 60%. Although the trial did not compare FOLFIRI to another cytotoxic regimen, the favorable survival rate suggests that FOLFIRI may be a viable option for second-line treatment.

Alongside irinotecan-based regimens, oxaliplatin-based therapies such as 5-fluorouracil, leucovorin (FOLFOX) are also regarded as viable options, with a reported response rate of 29%, median PFS of 4.5 months, and OS of 9.9 months.[9] A previous study focusing on the second-line therapies dacarbazine and temozolomide-based treatment reported a median PFS of 3 months and median OS of 7.2 months.[10] Studies on other regimens such as topotecan and lipotecan have shown similarly modest results along with substantial toxicity, and consequently, their use is generally not recommended.[11,12]

Study aim

Due to the lack of standard recommendations for second-line treatment of NEC, we conducted this retrospective study to evaluate the efficacy and outcomes of various second-line therapies administered after disease progression of first-line platinum/etoposide treatment. This study aims to provide a comprehensive analysis of patient responses, survival outcomes, and treatment-related toxicities across a range of therapeutic regimens.

Materials and Methods

Study design and setting

This retrospective cohort study enrolled patients diagnosed between January 2016 and June 2023 at Taipei Veterans General Hospital in Taiwan. The primary objective was to evaluate the efficacy of various treatments following disease progression after platinum and etoposide therapy. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital (Approval No. 2024-07-023CC, Approval date Aug 22, 2024). The patient's informed consent was waived by the IRB.

Participants

Participants eligible for the study were individuals aged 18 years or older diagnosed with extrapulmonary NEC. Data were collected from medical records, including the date of diagnosis, age, sex, histological information, date of death or last follow-up, previous chemotherapy treatments, pathology reports, and imaging results.

Outcome measures

The Response Evaluation Criteria in Solid Tumors version 1.1 was used to assess the objective response rate (ORR) and PFS of chemotherapy. OS was determined as the time from the date of initiation of chemotherapy to the patient's death from any cause. PFS was calculated from the date of initiation of chemotherapy to the occurrence of progressive disease or death.

Statistical analysis

Continuous variables were expressed as means ± standard deviation, and categorical variables as percentages. *T*-tests were applied to compare baseline continuous variables across groups receiving different regimens. Categorical variables were evaluated using the Chi-square test. Statistical analysis was performed with SPSS version 26 (IBM Inc., Armonk, NY, USA), and a $P < 0.05$ was considered statistically significant. Survival curves were plotted using the Kaplan–Meier method, and differences in survival among the groups were analyzed using the log-rank test. Both univariate and multivariate Cox regression analyses were conducted to assess the relationships between key clinical factors with PFS and OS, presenting the results as hazard ratios (HRs) alongside 95% confidence intervals (CIs).

Table 1: Baseline demographic and clinical characteristics

Characteristics	All (*n*=34), *n* (%)	FOLFOXIRI (*n*=9), *n* (%)	FOLFIRI (*n*=11), *n* (%)	FOLFOX (*n*=7), *n* (%)	Nivolumab + Ipilimumab (*n*=7), *n* (%)	*P*
Age, mean±SD	60.4±15.8	52.3±9.8	65.2±12.6	66.0±6.54	50.4±19.8	0.13
Age ≥65	13 (38.2)	0	5 (45.6)	5 (71.4)	2 (28.6)	0.02*
Male sex	25 (73.5)	8 (88.9)	7 (63.6)	4 (57.1)	6 (85.7)	0.37
ECOG status						0.83
0	25 (73.5)	8 (88.9)	9 (81.8)	5 (71.4)	3 (42.6)	
1	3 (8.8)	0	2 (18.2)	1 (14.3)	0	
2	2 (5.9)	1 (11.1)	0	1 (14.3)	1 (14.3)	
NA	3 (8.8)	0	0	0	3 (42.6)	
Primary site						0.09
Pancreas	8 (23.5)	3 (33.3)	3 (27.2)	0	2 (28.6)	
Biliary tract	6 (17.6)	1 (11.1)	1 (9.1)	4 (57.1)	0	
Colon	7 (20.6)	2 (22.2)	2 (18.2)	1 (14.3)	2 (28.6)	
Stomach	4 (11.8)	2 (22.2)	0	1 (14.3)	1 (14.3)	
Esophagus	2 (5.9)	0	0	1 (14.3)	1 (14.3)	
Unknown	4 (11.8)	0	4 (36.4)	0	0	
Other (≤1 cases)	3 (8.8)	1 (11.1)	0	0	1 (14.3)	
Metastasis site						0.64
Peritoneum	9 (26.4)	3 (35.7)	3 (27.3)	2 (28.6)	1 (14.3)	
Bone	5 (14.7)	0 (14.3)	3 (27.3)	0	2 (28.6)	
Liver	24 (70.6)	6 (92.8)	8 (72.7)	6 (85.7)	4 (57.1)	
Brain	1 (2.9)	0	1 (9.1)	0	0	
Lung	9 (26.5)	0 (21.3)	5 (45.5)	2 (28.6)	2 (28.6)	
Ki-67 index, mean±SD	74.6±16.8	76.5±16.0	76.7±17.5	73.3±16.3	66.6±25.1	0.83
>55%	20 (58.8)	6 (66.7)	7 (63.6)	5 (71.4)	2 (28.6)	0.33
NA	7 (20.6)	2 (7.1)	3 (27.2)	1 (14.3)	4 (57.1)	
1st line ORR	13 (38.2)	3 (33.3)	3 (27.2)	4 (57.1)	3 (42.9)	0.62
1st line mPFS (months)	5.9	3.6	5.5	9.0	8.1	<0.01

NA: Not available, SD: Standard deviation, ECOG: Eastern cooperative oncology group performance status, FOLFOXIRI: 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan, FOLFIRI: 5-fluorouracil, leucovorin, and irinotecan, FOLFOX: 5-fluorouracil, leucovorin, and oxaliplatin, ORR: Objective response rate, mPFS: Median progression-free survival. The symbol "*" in the table indicates the value is significant

Results

Patient characteristics

The baseline demographic and clinical characteristics of the 34 patients enrolled in this study are presented in Table 1 and analyzed across four treatment groups: 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI), FOLFIRI, FOLFOX, and Nivolumab + Ipilimumab. The average age of the participants was 60.4 years. A statistically significant difference was observed in the proportion of patients aged 65 years and older among the groups (P = 0.02), with the highest percentage noted in the FOLFOX group (71.4%). The primary sites of tumors varied, with liver metastases being the most prevalent (70.6%), followed by peritoneum and lung metastases. The mean Ki-67 proliferation index across all patients was 74.6%, with no significant differences between treatment groups. The ORR for first-line treatment with cisplatin/etoposide showed no significant difference across the groups. However, the median PFS varied significantly (P < 0.01), with the FOLFOX group achieving the longest median PFS at 9.0 months, compared to the shortest median PFS of 3.6 months in the FOLFOXIRI group.

Therapeutic efficacy

Table 2 presents the therapeutic efficacy of the different treatment regimens among the 34 patients. The median PFS and OS varied significantly across the treatment groups. Figure 1a and b show the Kaplan–Meier plots for median PFS and OS among the four groups. The FOLFOXIRI group demonstrated the longest median PFS at 4.1 months and median OS at 9.7 months. Regarding the response, no complete responses were observed in any group. The ORR was highest in the FOLFOXIRI group at 33.3%, with a disease control rate of 66.7%. In contrast, the disease progression rate in the Nivolumab + Ipilimumab group was 100%. We then compared the FOLFOXIRI group with the other three groups. Figure 2a and b show the Kaplan–Meier plots for median PFS and median OS, respectively. The FOLFOXIRI group still demonstrated significantly longer median PFS and OS compared to the other three groups.

Figure 3a and b illustrate the results of the univariate Cox regression analysis for factors influencing PFS and OS. The FOLFOXIRI group was significantly associated with improved survival outcomes, with a HR of 0.23 (95% CI: 0.09–0.58, P = 0.002) for PFS and 0.26 (95% CI: 0.10–0.71, P = 0.009) for OS. Other variables including age >65 years, PFS >180 days after first-line

Table 2: Therapeutic efficacy

Variables	All (*n*=34)	FOLFOXIRI (*n*=9)	FOLFIRI (*n*=11)	FOLFOX (*n*=7)	Nivolumab + Ipilimumab (*n*=7)
Survival					
mPFS (months), range	2.4 (0.5–7.8)	4.1 (2.3–7.8)	1.9 (1.0–2.4)	3.2 (2.1–5.4)	1.6 (0.5–3.5)
mOS (months), range	4.7 (0.5–23.2)	9.7 (3.2–23.2)	3.4 (1.0–14.3)	6.4 (5.0–15.4)	1.6 (0.5–9.7)
Best response, *n* (%)					
CR	0	0	0	0	0
PR	6 (17.6)	3 (33.3)	1 (9.1)	2 (28.5)	0
SD	5 (14.7)	3 (33.3)	1 (9.1)	1 (14.3)	0
PD	23 (67.6)	3 (33.3)	9 (81.8)	4 (57.1)	7 (100)
ORR (CR + PR)	6 (17.6)	3 (33.3)	1 (9.1)	2 (28.5)	0
DCR (CR + PR + SD)	11 (32.4)	6 (66.7)	2 (18.2)	3 (42.9)	0

mPFS: Median progression free survival, mOS: Median overall survival, CR: Complete response, PR: Partial response, ORR: Objective response rate, DCR: Disease control rate, FOLFOXIRI: 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan, FOLFIRI: 5-fluorouracil, leucovorin, and irinotecan, FOLFOX: 5-fluorouracil, leucovorin, PD: Progress disease, SD: Stable disease

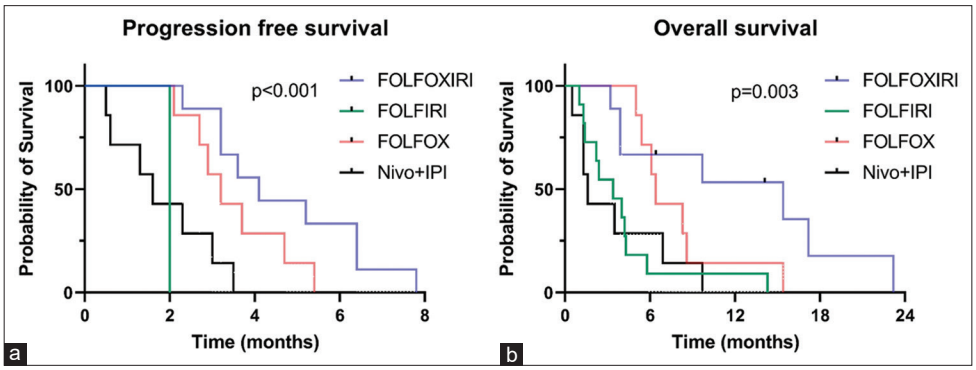

Figure 1: (a) Progression free survival among patient among four groups. (b) Overall survival among patient among four groups

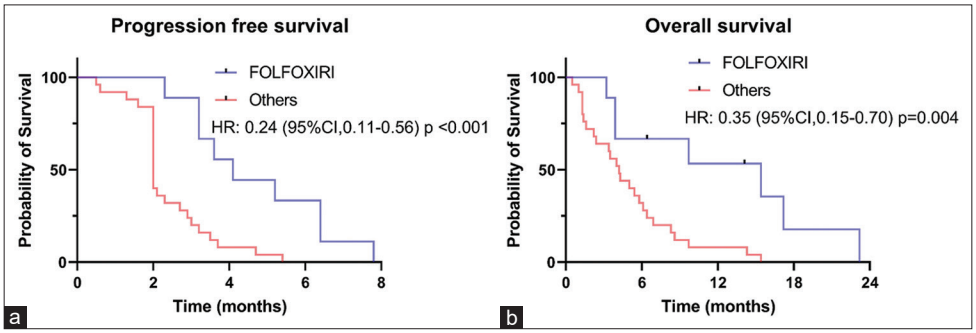

Figure 2: (a) Progression free survival of 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) group comparison with the other three groups, (b) Overall survival of FOLFOXIRI group comparison with the other three groups

EP treatment, ECOG performance status ≥2, Ki-67 index >55%, and response to EP were not significantly associated with survival.

In the multivariate Cox regression analysis [Figure 4a and b], the FOLFOXIRI group continued to demonstrate better survival outcomes after adjusting for clinically relevant confounding factors, including age >65 years and ECOG performance status ≥2. The HRs were 0.17 (95% CI: 0.06–0.48, $P = 0.001$) for PFS and 0.26 (95% CI: 0.09–0.78, $P = 0.017$) for OS.

Adverse effects

Table 3 shows the incidence of Grade 3–5 adverse events among the 34 patients. Overall, 35.3% of the patients experienced Grade 3 adverse events, with the highest occurrence in the FOLFOXIRI group (44.4%). Hematological toxicities were reported in 23.5% of the patients across all four groups, and body weight loss was the most observed adverse effect. Notably, no Grade 4 adverse events were reported in any treatment group.

Discussion

In this retrospective study, we evaluated the efficacy and safety of various second-line treatment regimens in patients with extrapulmonary NECs who had progressed after first-line platinum/etoposide therapy. Among the four treatment groups – FOLFOXIRI, FOLFIRI, FOLFOX,

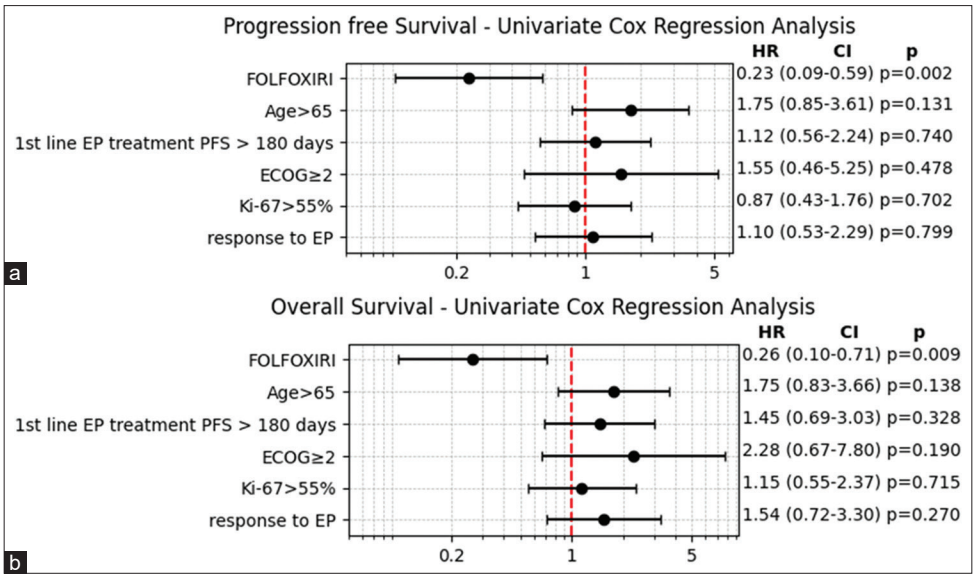

Figure 3: (a) Univariate Cox regression analysis for progression-free survival. (b) Univariate Cox regression analysis for overall survival

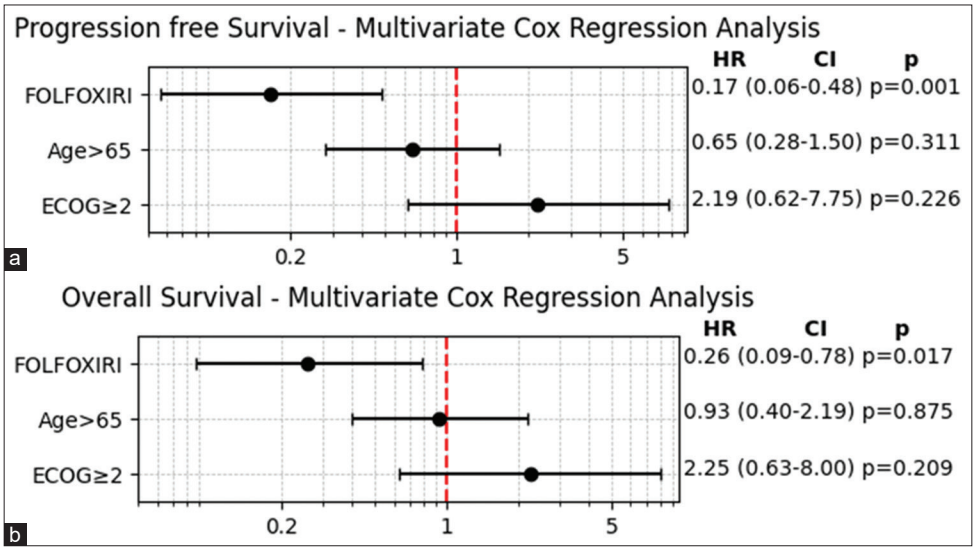

Figure 4: (a) Multivariate Cox regression analysis for progression-free survival. (b) Multivariate Cox regression analysis for overall survival

and Nivolumab + Ipilimumab – the FOLFOXIRI regimen yielded the most favorable outcomes, with a median PFS of 4.1 months and median OS of 9.7 months. However, the FOLFOXIRI group also had the highest incidence of Grade 3 adverse events.

Second-line chemotherapy for NECs has historically shown limited efficacy, with poor outcomes reported across various regimens in the literature.[8,9,12] A prior study assessed treatments including topotecan, paclitaxel, temozolomide, irinotecan, and combinations of paclitaxel with topotecan.[7] To the best of our knowledge, this is the first study to compare different commonly used 5-FU-based cytotoxic regimens and dual immunotherapy. Our results demonstrated that FOLFOXIRI offered better outcomes compared to the other groups, although its application as a second-line treatment for NECs remains underreported. For instance, the largest retrospective study to date, which treated 37 patients with gastroenteropancreatic NECs (GEP-NECs) using FOLFOXIRI as a first-line therapy, reported an ORR of 46% and a median OS of 17.8 months.[13] In contrast, our investigation, focusing on second-line therapy, observed a median OS of 9.7 months and an ORR of 33.3% in the FOLFOXIRI group.

The phase 2 NET-02 study of 58 patients with extrapulmonary NECs evaluated nal-IRI/5-FU versus docetaxel as second-line therapy.[14] A modest ORR of 10.3% was noted in the nal-IRI/5-FU arm, along with a median PFS of 3 months and median OS of 9 months. Similarly, the PRODIGE 41-BEVANEC phase 2 trial, which randomized 126 patients with advanced GEP-NECs or of unknown origin to receive FOLFIRI with or without bevacizumab, and the results showed no significant improvement in PFS or OS with the addition of bevacizumab.[8] The FOLFIRI alone arm reported a median

Table 3: Grade 3–5 adverse events

Grade 3–5 adverse events	All (*n*=34)	FOLFOXIRI (*n*=9)	FOLFIRI (*n*=11)	FOLFOX (*n*=7)	Nivolumab + Ipilimumab (*n*=7)
Any adverse events ≥3					
Grade 3	11 (32.4)	4 (44.4)	3 (27.3)	2 (28.6)	2 (28.6)
Grade 4	0	0	0	0	0
Hematological					
Leukopenia	2 (5.9)	1 (11.1)	1 (9.1)	0	0
Anemia	3 (8.8)	1 (11.1)	0	1 (14.3)	1 (14.3)
Thrombocytopenia	3 (8.8)	1 (11.1)	2 (18.2)	0	0
Renal and electrolyte imbalance					
Creatinine increased	1 (2.9)	0	0	1 (14.3)	0
Hypokalemia	4 (11.8)	2 (22.2)	2 (18.2)	0	0
Hyponatremia	4 (11.8)	2 (22.2)	1 (9.1)	0	0
Liver function disturbances	1 (2.9)	0	2 (18.2)	0	1 (14.3)
Diarrhea	2 (5.9)	1 (11.1)	1 (9.1)	0	0
Body weight loss	11 (32.4)	4 (44.4)	1 (9.1)	2 (28.6)	1 (14.3)

Data are presented as *n* (%). FOLFOXIRI: 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan, FOLFIRI: 5-fluorouracil, leucovorin, and irinotecan, FOLFOX: 5-fluorouracil, leucovorin

PFS of 3.5 months, a median OS of 8.9 months, and an ORR of 18.3%.

The effectiveness of immunotherapy as a first-line treatment for extrapulmonary NECs has not yet been established, but its potential in the second-line setting has been explored in numerous studies. The DART study used a combination of ipilimumab and nivolumab in 32 patients with non-pancreatic high-grade NECs and achieved an ORR of 44% and a 6-month PFS of 44%.[15] In contrast, the DUNE study evaluated durvalumab and tremelimumab across four neuroendocrine tumor cohorts, including patients with Grade 3 NECs, and reported a median OS of 5.4 months and an ORR of 9.1%.[16] Similarly, the AVENEC trial enrolled 29 patients with Grade 3 NENs treated with avelumab, and reported a disappointing 6.9% response rate and median OS of 7 months. Moreover, the patients with NECs achieved a median OS of 4.7 months.[17] Furthermore, a study assessing pembrolizumab in 29 patients with grade 3 extrapulmonary NENs, including 19 with NECs, reported an even lower ORR of 3.4%, with a median PFS of 2.2 months and median OS of 5.1 months.[18]

In our study, the seven patients treated with the combination of nivolumab and ipilimumab did not exhibit any responses, with a median OS of only 1.6 months. Our results highlight the limited effectiveness of the combination of nivolumab and ipilimumab in this patient population. This further emphasizes the need to identify biomarkers or other factors that can predict which patients are most likely to benefit from dual immunotherapy.

Our study had several limitations. First, the retrospective nature of the study introduces inherent biases, and there were significant differences in baseline characteristics across the four treatment groups. Notably, no patients in the FOLFOXIRI group were over 65 years of age, with a mean age of 52.3 years compared to 60.4 years across all groups. This age difference may mean that the patients in the FOLFOXIRI group were more tolerant of the toxic chemotherapy regimen. Second, the median PFS following first-line treatment with cisplatin/etoposide was significantly shorter in the FOLFOXIRI group. This suggests that the patients in this group may have had more aggressive disease, which, combined with their younger age, may have influenced the decision to use the more intensive FOLFOXIRI regimen. Third, although the ECOG performance status was not significantly different across groups before treatment, patients selected for dual immunotherapy with nivolumab and ipilimumab may have had more comorbidities or appeared more frail, leading the physicians to opt for immunotherapy over chemotherapy. This may have contributed to patient selection bias, further complicating the interpretation of our results.

Despite these limitations, our results suggest that the FOLFOXIRI regimen has the potential to become the most effective second-line treatment for patients with extrapulmonary NECs who have progressed after first-line platinum/etoposide therapy.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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Conflicts of interest

There are no conflicts of interest.

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