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Original Article

Efficacy of atezolizumab combined with platinum and etoposide in the treatment of extrapulmonary neuroendocrine carcinoma

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Abstract

Background: Neuroendocrine carcinoma (NEC) is an aggressive, poorly differentiated Grade 3 (G3) tumor with high nuclear and cellular atypia and Ki-67 indices over 20%. While most cases are lung NECs, extrapulmonary NECs are rarer and less studied. Standard treatment involves etoposide and platinum (EP) chemotherapy. Inspired by the IMpower133 study, which showed survival benefits with atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer, this study investigates whether atezolizumab combined with platinum and etoposide can offer similar benefits for extrapulmonary NEC.

Method: This retrospective cohort study, conducted at Taipei Veterans General Hospital from January 2016 to June 2023, compared the efficacy of atezolizumab combined with platinum and etoposide versus standard chemotherapy alone in extrapulmonary NEC patients. The outcomes assessed were response rate, progression-free survival (PFS), and overall survival (OS).

Result: The study evaluated 56 patients: 14 received atezolizumab with platinum and etoposide (EP), while 42 were treated with EP alone. The median PFS was 5.2 months, and median OS was 11.9 months for the whole cohort. While there were no significant differences in OS or PFS between the groups, the response rate was significantly higher in the atezolizumab group. Additionally, a neutrophil-lymphocyte ratio (NLR) above 3 was linked to poorer OS.

Conclusion: The addition of atezolizumab to EP did not improve PFS and OS in extrapulmonary NEC patients but did result in a higher response rate. Moreover, an NLR above 3 at diagnosis was identified as a poor prognostic factor for OS.

Key words: atezolizumab; extrapulmonary neuroendocrine carcinoma; platinum; etoposide; progression-free survival; overall survival; neutrophil-lymphocyte ratio; immunotherapy.

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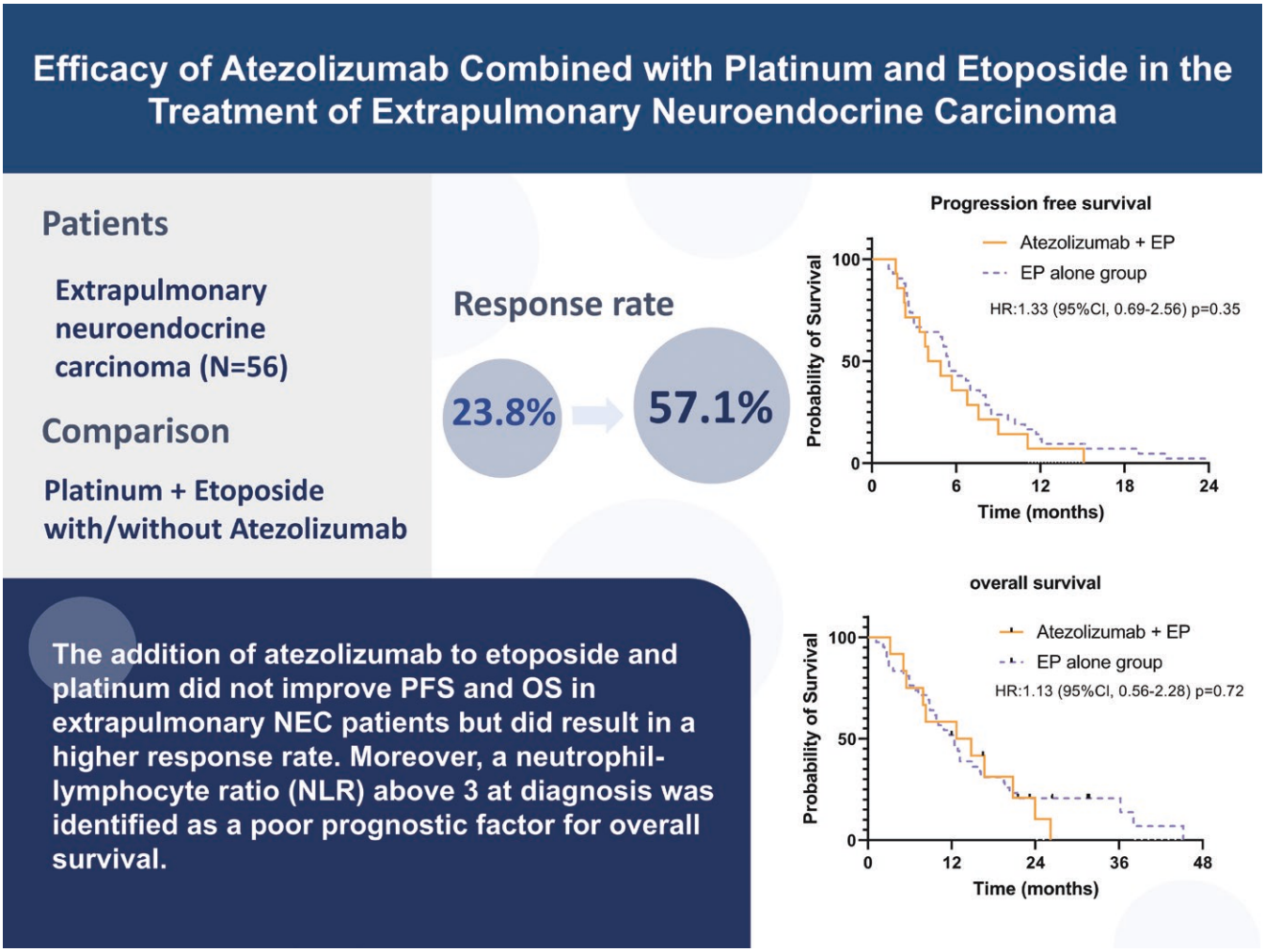
Graphical Abstract



Implications for Practice

The addition of atezolizumab to etoposide and platinum did not significantly improve overall survival and progression-free survival in patients with extrapulmonary neuroendocrine carcinomas. However, atezolizumab demonstrated a notable increase in response rates. Given these findings, further clinical trials investigating the use of atezolizumab in neoadjuvant settings for borderline resectable extrapulmonary NEC may be warranted.

Background

Neuroendocrine neoplasms (NENs) are classified by the 2022 World Health Organization as either well-differentiated tumors or poorly differentiated carcinomas based on morphological characteristics and proliferation markers, notably the Ki-67 index.[1] Neuroendocrine carcinomas (NECs) are categorized as poorly differentiated and highly aggressive Grade 3 (G3) NENs, characterized by significant nuclear and cellular atypia, severe nuclear molding, and retention of neuroendocrine markers. The Ki-67 proliferation index in NECs is typically ≥20%, often exceeding 50%.[2] Lung NECs are the most prevalent subtype among poorly differentiated NECs, accounting for 91.3% of cases and are well-characterized.[3] Conversely, extrapulmonary NECs are rare, and due to the scarcity of prospectively collected data, treatment guidelines are largely derived from expert opinions and adaptations from lung small-cell carcinoma management strategies.[4,5]

First-line chemotherapy for advanced NECs usually includes a combination of etoposide and platinum (EP)-based chemotherapy.[4,5] In the largest reported cohort, response rate reported 31%.[6] Patients with a Ki-67 index below 55% exhibited a lower response rate compared with those with an index of 55% or higher (15% vs 42%), yet they experienced better survival outcomes (14 vs 10 months). Studies have suggested that cisplatin might be substitutable with the less toxic carboplatin, given their comparable efficacy.[6]

The efficacy of immunotherapy in the first-line treatment of extrapulmonary NECs remains unproven. However, in the second line setting for extrapulmonary NECs, its use might be viable. The DART study documented a 44% objective response rate (ORR) using a combination of ipilimumab and nivolumab in patients with nonpancreatic high-grade NEC.[7] In contrast, the DUNE study reported only a limited response with the combination of durvalumab and tremelimumab

across 4 NEN cohorts, including G3 NEN, where the median overall survival (OS) was 5.4 months, and the ORR was 9.1%.[8] Given the mixed outcomes observed in previous trials, and drawing inspiration from the success of the IMpower133 study, which demonstrated significant survival benefits with atezolizumab combined with chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer—reporting a median OS of 12.3 months in the atezolizumab group compared with 10.3 months in the chemotherapy-alone group, and a median progression-free survival (PFS) of 5.2 months versus 4.3 months—we were prompted to initiate a retrospective study.[9] This study aims to assess the efficacy of atezolizumab combined with platinum and etoposide in treating extrapulmonary NEC. Our goal is to determine if similar benefits can be achieved in this distinct and challenging patient population, potentially offering new avenues for effective treatment strategies.

Methods

Study design and setting

This retrospective cohort study was conducted at Taipei Veterans General Hospital, Taiwan, from January 2016 to June 2023. The primary objective of the study was to compare the efficacy of atezolizumab combined with platinum and etoposide against chemotherapy alone. Additionally, data from next-generation sequencing were also analyzed. The study received approval from the Institutional Review Board of Taipei Veterans General Hospital (Approval No. 2024-07-023CC).

Participants

Eligible participants were individuals aged 18 years or older who had been diagnosed with extrapulmonary NEC. Data extracted from medical records included the date of diagnosis, age, sex, histological details, date of death or last follow-up, previous chemotherapy regimens, pathology report, imaging studies, and next-generation sequencing reports.

Treatment regimen

Patients followed a standard treatment consisting of 21-day cycles of carboplatin (administered intravenously at an area under the curve of 4-6 mg/mL/minute on day 1 of each cycle) or cisplatin (75 mg/m², which could be divided into 25 mg/m² over 3 days in combination with etoposide). Etoposide was administered intravenously at a dose of 100 mg/m² on days 1 through 3 of each cycle, with or without the addition of atezolizumab (1200 mg, fixed dose, administered intravenously on day 1 of each cycle).

Outcome measures

The primary endpoints of this study were PFS and OS, while ORR was assessed as a secondary exploratory endpoint. PFS was defined as the time from the initiation of chemotherapy to the occurrence of progressive disease (PD) or death from any cause, and OS was defined as the period from the start of chemotherapy to the patient's death from any cause. ORR was evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1 to determine the proportion of patients achieving complete or partial response.[10] Imaging was typically performed every 3- RECIST RECIST RECIST RECIST4 months as part of routine clinical practice, unless there were indications of clinical disease progression.

Statistical analysis

Continuous variables were represented as means ± SD, and categorical variables were reported as percentages. The differences in continuous variables between the Atezolizumab plus EP combination group and the EP alone group were analyzed using the *t*-test. Categorical variables were evaluated with the Chi-square test. Statistical analyses were performed using SPSS software, version 26. A *P*-value of <.05 was considered to indicate statistical significance. Survival curves were constructed using the Kaplan–Meier method, and differences in survival between groups were assessed using the log-rank test. Both univariate and multivariate Cox regression analyses were employed to explore the associations between relevant characteristics and both PFS and OS, with results presented as hazard ratios (HRs) and 95% CIs.

Results

In this study, we evaluated the baseline demographic and clinical characteristics of participants, as summarized in Table 1. The cohort included patients treated with atezolizumab in combination with EP ($N = 14$) and those treated with EP alone ($N = 42$). There were no statistically significant differences between the groups in terms of median age (58.8 ± 12.3 years for the combination therapy group versus 64.4 ± 14.8 years for the EP alone group; $P = .343$), gender distribution (64.3% male in both groups; $P = 1.0$), and ECOG performance status ($P = .373$). Additionally, the distribution of primary cancer sites and metastatic sites did not differ significantly between the 2 treatment groups. The Ki-67 proliferation index, an indicator of cell proliferation, was comparable between the groups, with a mean ± SD of 79.6 ± 17.1 in the atezolizumab plus EP group versus 76.7 ± 18.5 in the EP alone group ($P = .4$).

Therapeutic efficacy outcomes, detailed in Table 2, showed that across all patients ($N = 56$), the median progression-free survival (mPFS) was 5.2 months (range 1.2-31.7 months), and the median overall survival (mOS) was 11.9 months (range 1.2-45.2 months). For the group receiving atezolizumab plus EP, mPFS was 4.5 months (range 1.7-15.1 months), and mOS was 10.9 months (range 3.2-26.2 months). Patients receiving EP alone exhibited mPFS and mOS at 5.5 months (range 1.2-31.7 months) and 11.9 months (range 1.2-45.2 months), respectively. Kaplan–Meier plots (Figure 1A and B) reveal no significant difference in OS (HR 1.13, 95% CI, 0.56-2.28, $P = .72$) or PFS (HR 1.33, 95% CI, 0.69-2.56, $P = .35$) between the 2 groups.

The best response observed showed that complete response (CR) was achieved in 1.9% of all patients, with no CRs in the atezolizumab plus EP group and one in the EP alone group. Partial response (PR) rates were higher in the combination therapy group (57.1%) compared with the EP alone group (21.4%). Stable disease (SD) was reported in 25.9% of all patients, while PD was observed in 38.9%. The ORR in the combination therapy group was 57.1%, higher than 23.8% in the EP alone group. Similarly, the disease control rate (DCR) was 71.4% in the combination therapy group compared with 52.4% in the EP alone group.

Figure 2A and B presents the univariate Cox regression analysis results for factors impacting OS and PFS. Lactate dehydrogenase (LDH) levels above the upper limit of normal (HR 2.39, 95% CI, 1.29-4.41, $P = .005$) and a neutrophil-to-lymphocyte ratio (NLR) greater than 3 (HR 2.58, 95%

Table 1. Baseline demographic and clinical characteristics.

Characteristics	All (*N* = 56)	Atezolizumab + EP (*N* = 14)	EP alone (*N* = 42)	*P*-value
Age				
Median ± SD	62.2 ± 13.9	58.8 ± 12.3	64.4 ± 14.8	.343
Age ≥ 65 years, No. (%)	24 (42.9)	4 (28.5)	20 (47.6)	.35
Male sex, No. (%)	36 (64.3)	9 (64.3)	27 (64.3)	1.0
ECOG performance status				.373
0	38 (67.9)	10 (71.4)	28 (66.7)	
1	11 (19.6)	4 (28.6)	7 (16.7)	
2	4 (7.14)	0 (0)	4 (9.5)	
Not available	3 (5.4)	0 (0)	3 (7.1)	
Primary site, No. (%)				.14
Pancreas	11 (19.6)	6 (42.9)	5 (11.9)	
Biliary tract	8 (14.3)	3 (21.4)	5 (11.9)	
Colon	8 (14.3)	2 (14.3)	6 (14.3)	
Stomach	6 (10.7)	1 (7.1)	5 (11.9)	
Esophagus	3 (5.4)	0 (0)	3 (7.1)	
genitourinary tract	7 (12.5)	0 (0)	7 (16.7)	
Unknown (Not lung)	8 (14.3)	2 (14.3)	6 (14.3)	
Other (≤2 cases)	5 (8.9)	0 (0)	5 (11.9)	
Metastasis site				.78
Peritoneum	19 (33.9)	5 (35.7)	14 (25)	
Bone	9 (16.1)	2 (14.3)	7 (12.5)	
Liver	36 (64.3)	13 (92.8)	23 (41.1)	
Brain	1 (1.8)	0 (0)	1 (1.8)	
Lung	13 (23.2)	3 (21.3)	10 (17.6)	
Ki-67 index				
Mean ± SD (range)	80 ± 12.2	79.6 ± 17.1	76.7 ± 18.5	.4
>55%	37 (66.1)	11 (78.5)	26 (61.9)	.32
NA	11 (19.6)	1 (7.1)	10 (23.8)	
Cisplatin/Carboplatin (*N*)	43/13	11/3	32/10	1.0
Cumulative dose intensity[a]				
Platinum, mean (range)	0.90 (0.48-1.05)	0.91 (0.48-1.05)	0.90 (0.48-1.03)	.94
Etoposide, mean (range)	0.75 (0.36-1.01)	0.71 (0.36-0.9)	0.76 (0.38-1.01)	.23

Abbreviations: EP: Etoposide + platinum, *N* = number.
[a]Cumulative dose intensity: calculated as the cumulative actual dose divided by (standard dose × total cycles administered). The standard doses are cisplatin 75 mg/m² or carboplatin 5 AUC in day1 and etoposide 100 mg/m² on day 1 to day 3.

CI, 1.39-4.72, *P* =.002) were associated with poorer OS outcomes. Elevated LDH was also associated with shortened PFS (HR 1.81, 95% CI, 1.05-3.12, *P* =.033).

The multivariate Cox regression analysis results (Figure 3A and B) for OS indicated that the addition of atezolizumab to EP showed an adjusted HR of 1.55 (95% CI, 0.79-3.01, *P* =.19), demonstrating no statistically significant improvement in survival. However, an NLR greater than 3 was associated with a significantly higher risk of mortality (HR 2.24, 95% CI, 1.14-4.40, *P* =.02). For PFS, neither atezolizumab co-administration (HR 1.42, 95% CI, 0.76-2.63, *P* =.27) nor elevated LDH levels (HR 1.61, 95% CI, 0.86-3.01, *P* =.14) were associated with significant differences. An NLR greater than 3 also showed no significant impact on PFS (HR 1.35, 95% CI, 0.72-2.52, *P* =.35).

Table 3 details the incidence of Grades 3-5 adverse events in a cohort of 56 patients treated with either Atezolizumab plus EP or EP alone. Notably, 46.4% of participants encountered at least one Grade 3 or higher adverse event. Specific hematological complications included leukopenia in 21.4% of patients, anemia in 16.1%, and thrombocytopenia in 7.1%. Renal and electrolyte disturbances were observed as well, with 3.6% of patients showing increased creatinine levels, 7.1% experiencing both hypokalemia and hyponatremia, and 1.8% developing hyperkalemia.

Patient genetic alteration data were visualized in Figure 4, which organized genes as rows and samples as columns to display mutation counts. The analysis revealed the most frequent alteration genes, ranked by the summation of mutation counts across samples: TP53 (90%), RB1 (40%), FBXW7 (30%), and MLL2 (30%).

Discussion

This study is the first, to our knowledge, to evaluate the efficacy of combining platinum and etoposide with atezolizumab

Table 2. Therapeutic efficacy.

Variables	All patients ($N = 56$)	Atezolizumab + EP ($N = 14$)	EP alone ($N = 42$)	*P*-value
Survival				
mPFS (months), range (95% CI)	5.2 (1.2-31.7)	4.5 (1.7-15.1)	5.5 (1.2-31.7)	.35
mOS, (months), range (95% CI)	11.9 (1.2-45.2)	10.9 (3.2-26.2)	11.9 (1.2-45.2)	.72
Best response, No. (%)				
CR	1 (1.9)	0 (0.0)	1 (2.4)	
PR	17 (31.5)	8 (57.1)	9 (21.4)	
SD	14 (25.9)	2 (14.3)	12 (28.6)	
PD	21 (38.9)	4 (28.6)	19 (45.2)	
Not evaluable	1 (1.9)	0 (0.0)	1 (2.4)	
ORR (CR + PR)	18 (33.3)	8 (57.1)	10 (23.8)	.04
DCR (CR + PR + SD)	32 (59.3)	10 (71.4)	22 (52.4)	.35

Abbreviations: CR: complete response, DCR: disease control rate, mOS: median overall survival, mPFS: median progression-free survival, ORR: objective response rate, PR: partial response.

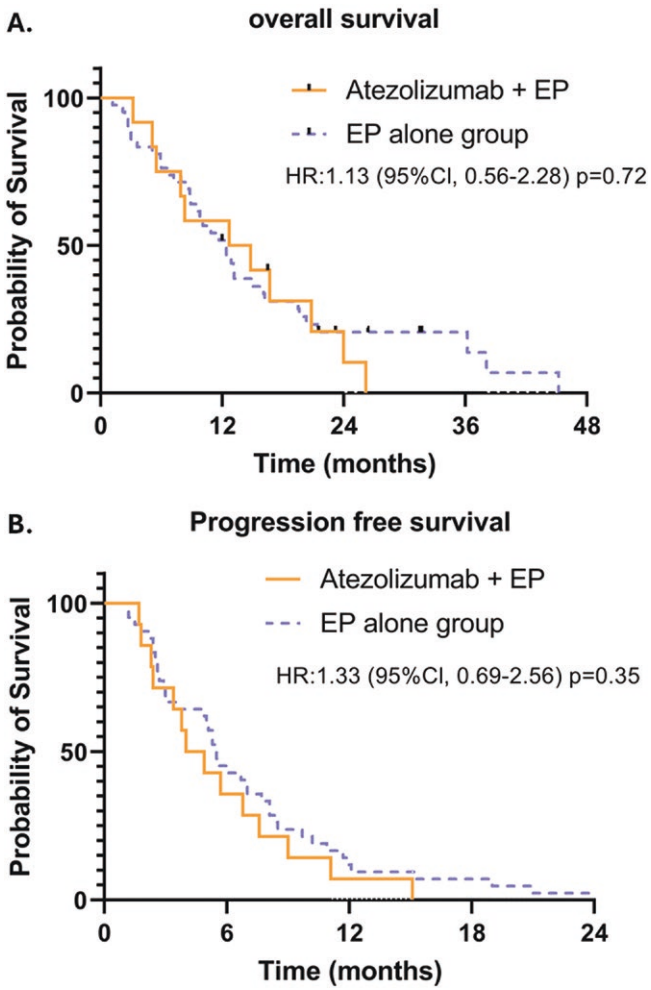


Figure 1. (A) Kaplan–Meier plot of progression-free survival comparing the addition of atezolizumab to etoposide and platinum (EP) versus EP alone. The hazard ratio (HR) is 1.33 (95% CI, 0.69-2.56), with a *P*-value of .35. (B) Kaplan–Meier plot of overall survival comparing the addition of atezolizumab to EP versus EP alone. The HR is 1.13 (95% CI, 0.56-2.28), with a *P*-value of .72.

in treating extrapulmonary NEC. Our findings suggest that the addition of atezolizumab did not significantly improve PFS or OS compared with the standard regimen of EP chemotherapy alone.

Extrapulmonary NECs are rare, and due to their scarcity, treatment protocols are often derived from small-cell lung cancer (SCLC) strategies.[4,5] Traditionally, cisplatin and etoposide have been considered first-line chemotherapy options for these tumors.[4,5] The largest cohort study, the NORDIC NEC, involving 252 patients with advanced gastrointestinal NEC, reported a response rate of 31%, with stable disease observed in 33% of patients, a median PFS of 4 months, and an OS of 11 months.[6] Other first-line chemotherapy regimens, such as those evaluated in the TOPIC-NEC Phase 3 Trial which included 170 patients with NEC arising from the gastrointestinal tract, hepatobiliary system, or pancreas, compared EP with irinotecan plus cisplatin (IP) and found no significant differences in median OS (12.5 months with EP vs 10.9 months with IP) or PFS (5.6 months with EP vs 5.1 months with IP).[11] Response rates were comparable (54.5% with EP vs. 52.5% with IP), though IP was associated with less hematologic toxicity, suggesting a viable alternative front-line therapy.

Contrasting the limited efficacy of standard chemotherapy in NECs, the advent of immunotherapy has revolutionized treatment for SCLC, the most common NEC.[3] The CASPIAN trial demonstrated that first-line treatment with durvalumab plus platinum-etoposide significantly improved OS in patients with ES-SCLC, with a median OS of 13.0 months in the durvalumab plus platinum-etoposide group versus 10.3 months in the control group.[12] Similarly, the IMpower133 trial reported a median OS of 12.3 months in the atezolizumab group compared with 10.3 months in the placebo group, with median PFS of 5.2 months versus 4.3 months, respectively.[9] These studies introduce new strategies for combining standard-of-care chemotherapy with EP agents as a frontline treatment for adult patients with ES-SCLC, offering new hope in the management of this challenging disease.

However, our findings indicate that the benefits observed in SCLC may not directly translate to extrapulmonary NECs in a first-line setting. Notably, 6 out of 14 patients in the immunotherapy group had pancreatic primary tumors. While pancreatic adenocarcinoma generally shows limited

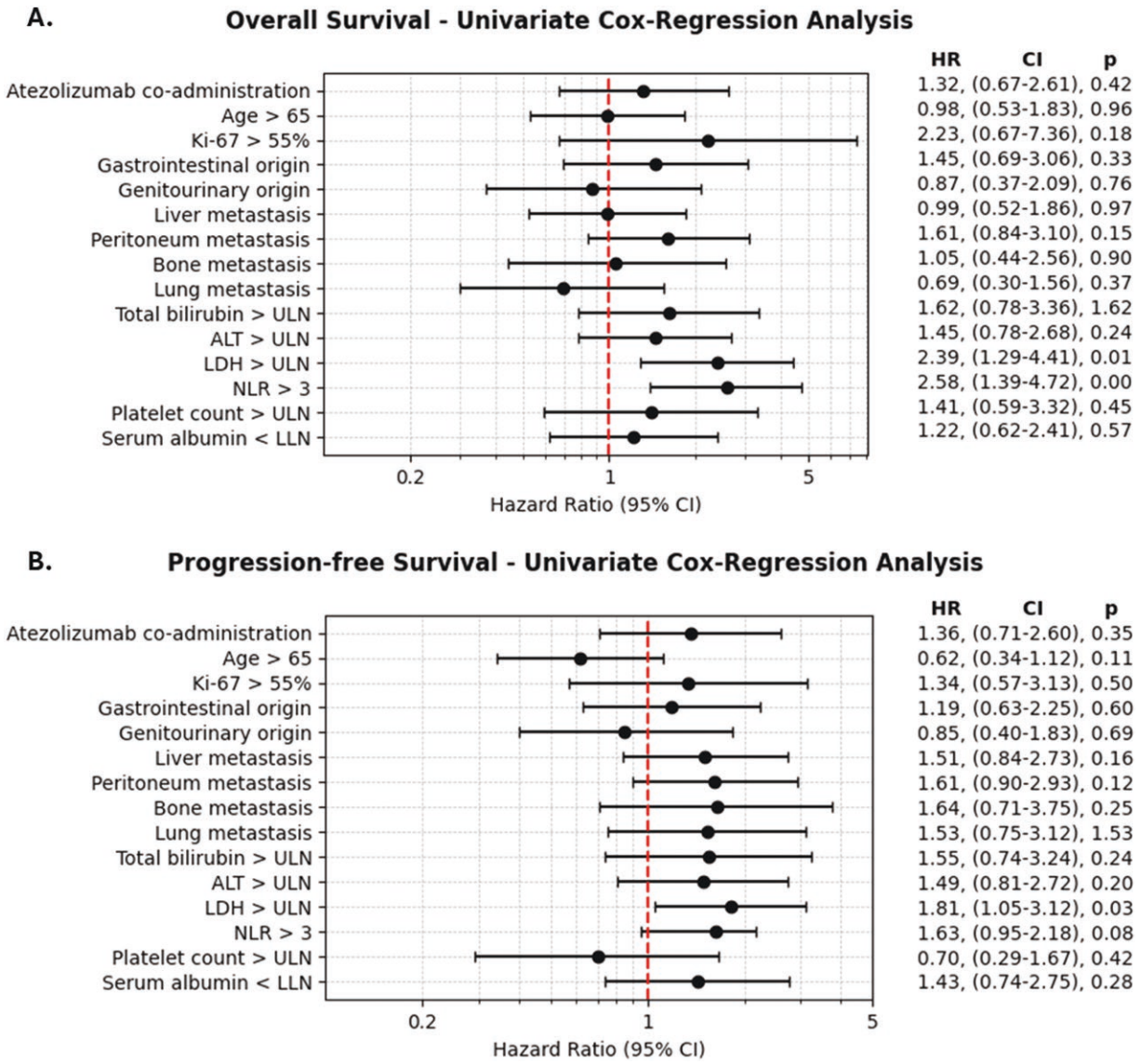


Figure 2. Forest plots of univariate Cox regression analyses for overall survival (A) and progression-free survival (B), illustrating the hazard ratios and 95% CIs for various clinical and demographic factors.

benefit from immunotherapy, our findings suggest that pancreatic NECs may exhibit a similar trend, likely due to their distinct tumor microenvironment and molecular characteristics. Elvebakken et al. also highlight the heterogeneity of high-grade GEP-NENs, showing that treatment outcomes can vary significantly by primary tumor site.[13] Molecular features such as BRAF and KRAS mutations have been shown to critically influence progression and survival, underscoring the importance of tailoring treatment strategies based on tumor biology.[13]

Immunotherapy in extrapulmonary NECs has shown limited results, though its effectiveness in pretreated patients is noteworthy. In the NIPI-NEC Phase II trial, which enrolled 185 patients with platinum-refractory disease, including 93 with GEP-NEC, the combination of nivolumab and ipilimumab showed a notable ORR of 14.9% compared with 7.2% in the monotherapy cohort.[14] Nevertheless, both PFS and OS were similar between the groups, suggesting that while immunotherapy may offer some clinical benefit, its impact on survival is limited.

A similar observation was reported in the NICE-NEC Phase II trial, which evaluated nivolumab in combination with platinum-based chemotherapy in 37 chemotherapy-naïve patients with advanced G3 GEP-NENs or unknown primary tumors.[15] The trial reported an ORR of 56.8%, median PFS of 5.7 months, and median OS of 13.9 months. However, the study did not meet its primary endpoint of improving the 12-month OS rate, although 37.6% of patients achieved long-term survival (>2 years), suggesting potential benefits in certain subgroups. In our study, a higher ORR (57% vs 23%) was also observed in the atezolizumab group; however, this improvement did not translate into better survival outcomes. While these findings suggest the potential of combining atezolizumab with chemotherapy in the neoadjuvant setting for patients with borderline resectable extrapulmonary NEC, this approach is not yet established and requires further investigation in larger, prospective studies.

Further insights come from the DART SWOG 1609 trial, which showed a 44% ORR in patients with nonpancreatic high-grade NEC when treated with the nivolumab and

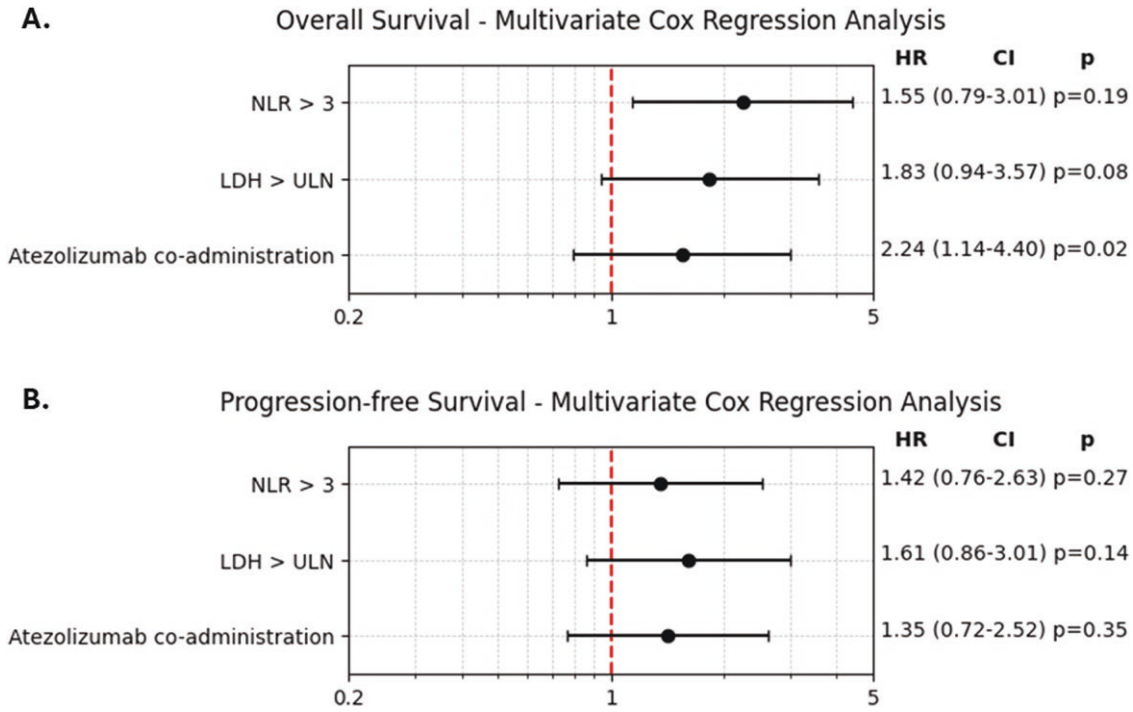


Figure 3. Forest plots of multivariate Cox regression analyses for overall survival (A) and progression-free survival (B), illustrating the hazard ratios and 95% CIs for various clinical and demographic factors.

Table 3. Grades 3-5 adverse events.

Grades 3-5 adverse events	All ($N = 56$)	Atezolizumab + EP ($N = 14$)	EP alone ($N = 42$)	*P*
Any adverse events ≥ 3				
Grade 3	26 (46.4)	6 (42.8)	20 (47.6)	1.0
Grade 4	1 (1.8)	0 (0)	1 (2.4)	1.0
Grade 5	0 (0)	0 (0)	0 (0)	
Hematological				
Leukopenia	12 (21.4)	2 (14.2)	10 (23.8)	.71
Anemia	9 (16.1)	3 (21.4)	6 (14.3)	.67
Thrombocytopenia	4 (7.1)	2 (14.2)	2 (2.4)	.26
Renal and electrolyte imbalance				
Creatinine increased	2 (3.6)	0 (0)	2 (4.8)	1.0
Hypokalemia	4 (7.1)	2 (14.2)	2 (4.8)	.26
Hyperkalemia	1 (1.8)	0 (0)	1 (2.4)	1.0
Hyponatremia	4 (7.1)	0 (0)	4 (9.5)	.56
Liver function disturbances	1 (1.8)	0 (0)	1 (2.4)	1.0
Body weight loss	11 (19.6)	3 (21.4)	8 (19.0)	1.0
Data are presented as *n* (%)				

ipilimumab combination, although the study had a small cohort of only 32 eligible patients, with 19% having lung primary sites.[7] A retrospective analysis of 42 metastatic EP-NEC cases, predominantly originating from GEP and with 11 receiving the dual immunotherapy, also achieving improved PFS and OS compared with those receiving ICI monotherapy or cytotoxic chemotherapy.[16] However, not all dual ICI therapies have elicited significant responses. In a study grouping cases based on grading and primary sites, the response rates and median PFS varied significantly across the cohorts, with no responses seen in G1/G2 gastrointestinal neuroendocrine tumors (GI-NETs) and pancreatic neuroendocrine tumors (pNETs), and only a modest survival benefit observed in G3 GEP-NENs or NEC cases.[8] The diverse outcomes across these cohorts underscore the challenge of applying a one-size-fits-all approach to immunotherapy in NEC.

To address these unmet clinical need, a new clinical trial (SWOG S2012) is underway, evaluating the efficacy of first-line treatment with platinum/etoposide (P/E) with or without atezolizumab in patients with poorly differentiated extrapulmonary NEC.[17] The outcomes of this trial are anticipated to provide further clarity on the role of immunotherapy as a

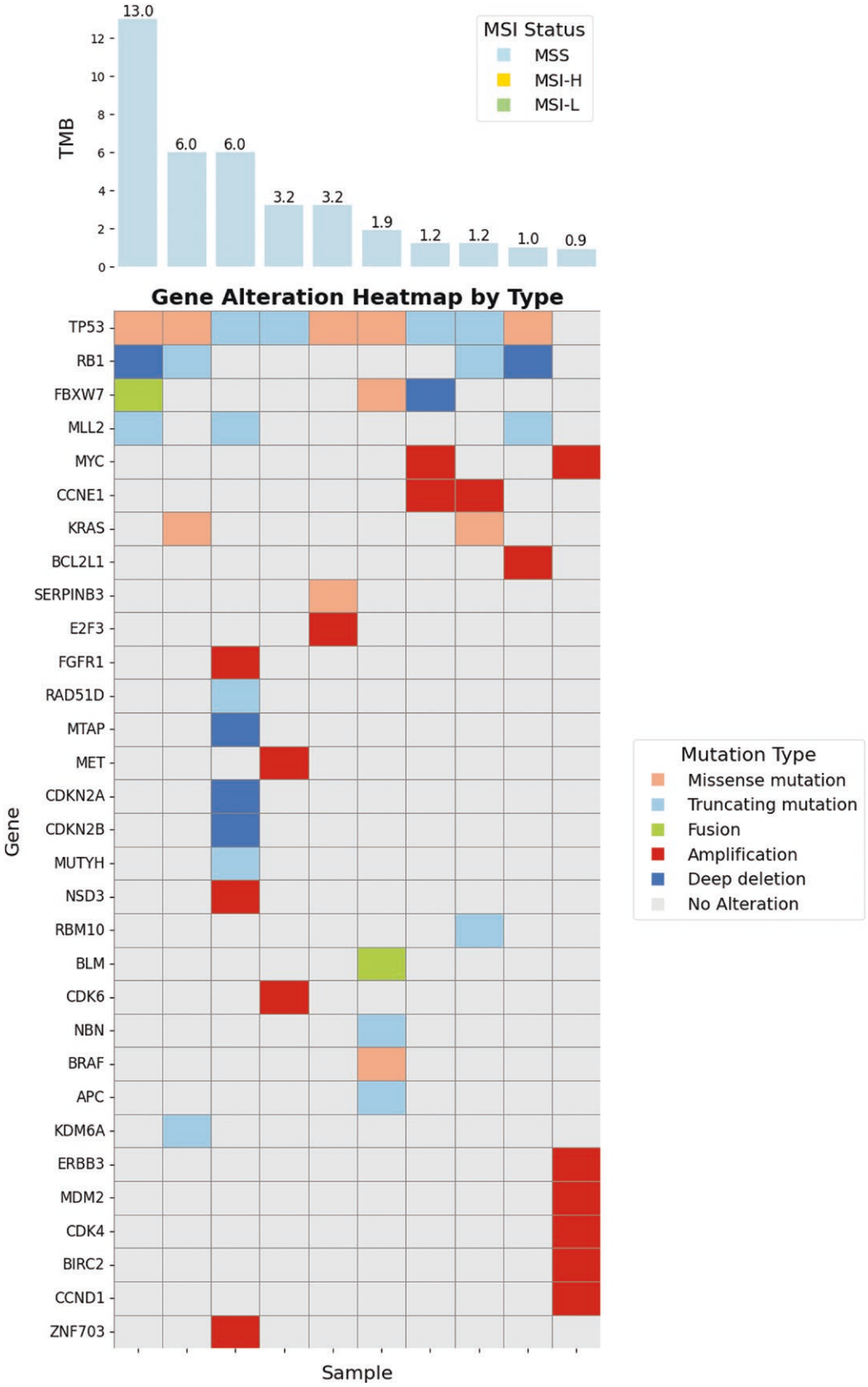


Figure 4. The figure shows a heatmap of gene alterations across multiple samples, with a bar chart above that illustrates the tumor mutational burden (TMB) for each sample. The TMB values are noted numerically on top of each bar for microsatellite stable samples. In the heatmap below, each row corresponds to a gene, and each column to an individual sample. Different types of gene alterations—such as missense mutations, truncating mutations, fusion events, amplifications, and deletions—are indicated by various patterns or markings, while lack of an alteration is shown with a separate pattern.

first-line treatment option and potentially redefine therapeutic strategies for this challenging group of cancers.

Additionally, novel agents targeting DLL3, such as BI 764 532 and tarlatamab, are being explored for their potential in treating extrapulmonary NECs. BI 764 532 is a bispecific DLL3/CD3 T-cell engager designed to bind DLL3-expressing tumor cells and activate immune cells against them.[18] Updated data from a Phase I trial presented at the ENETS annual conference in March 2024 reported an ORR of 26% in DLL3-positive extrapulmonary NECs, demonstrating promising efficacy.[19] This has led to the initiation of the DAREON-5 trial, which is currently investigating BI 764 532 in relapsed/refractory NECs.[20] Similarly, tarlatamab, another DLL3-targeting bispecific T-cell engager, is being evaluated in metastatic neuroendocrine prostate carcinoma.[21] These novel approaches hold promise for improving outcomes in patients with extrapulmonary NECs, particularly in biomarker-driven and molecularly targeted subsets.

Excessive inflammation is known to contribute to the development and progression of tumor cells.[22] The neutrophil-lymphocyte ratio (NLR) is recognized as a key marker of systemic inflammatory response in patients with cancer.[23] Neutrophils can suppress *t*-cell proliferation through mechanisms involving integrin Mac-1 and the release of hydrogen peroxide, which impairs the immune system's ability to combat tumor growth.[24] Conversely, lymphocytes play a vital role in tumor defense by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration.[25] Thus, a reduced number of lymphocytes leads to a weaker immune response against tumor cells. The NLR, therefore, provides critical insights into the inflammatory status and immune competence of a patient, influencing the overall tumor environment and potentially affecting patient outcomes.[26] There is an increasing evidence suggesting that an elevated NLR is associated with a poorer clinical outcome across various cancers.[27,28] Although a specific cutoff level for a high NLR is not universally defined, a value greater than 3 is commonly used.[29-31] Our studies corroborate these findings, demonstrating that an NLR greater than 3 serves as an independent poor prognostic factor for OS in both univariate and multivariate analyses. However, a high NLR did not correlate with poor prognosis in terms of PFS. NLR should be considered in future individual risk assessments in patients with NEC.

In our retrospective study, the adverse effects between the Atezolizumab plus EP group and the EP alone group were not significantly different. Notably, 46.4% of participants experienced at least one Grade 3 or higher adverse event, with no Grade 5 events reported. This incidence of adverse events is slightly lower than the 56% reported in the IMpower133 study, which could be attributed to the retrospective nature of our study potentially leading to some data loss.[9] The most prevalent side effect in our cohort was leukopenia, affecting 21.4% of all patients, aligning with the 23% reported in the IMpower133 study. These findings suggest that the tolerability profiles for these treatment regimens are consistent with previous research.

Whole-genome sequencing analysis has shown that mutations in TP53 and RB1 are nearly ubiquitous in SCLC, with reported prevalence rates of 100% and 93%, respectively.[32] However, the mutation spectrum in extrapulmonary NECs appears to be different. A study involving 143 GI-NECs revealed a distinct genomic landscape characterized by significant genetic heterogeneity across different anatomical locations.[33] Despite this variability, TP53 was the most frequently mutated gene, observed in 88.8% of cases, followed by RB1 at 25.2% and APC at 18.2%. Notably, 72.7% of patients harbored at least one clinically relevant actionable genetic alteration, with the most common mutations identified in genes such as CCNE1 (27.3%), RB1 (10.5%), APC (9.0%), KRAS (7.7%), CTNNB1 (7.0%), and ERBB2 (6.3%).[33]

In the context of other neuroendocrine tumors, mutation profiles vary considerably. For instance, among 24 cases of small-cell neuroendocrine cervical cancer, the most prevalent mutations were in PIK3CA (18%), KRAS (14%), and TP53 (11%).[34] A study of 14 patients with head and neck NECs identified TP53 (43%), RB1 (21%), and PIK3CA (14%) as the most common pathogenic mutations.[35] Prostate NECs, meanwhile, exhibit a distinct pattern characterized by genomic and epigenomic alterations, including the loss of RB1 (90%), loss of TP53 (67%), and ERG rearrangements (45%).[36] In our cohort, the most prevalent mutations included TP53 (90%), RB1 (40%), FBXW7 (40%), and MLL2 (30%). Approximately 60% of patients displayed potentially actionable alterations, with notable mutations in MTAP, CDK4/6, MDM2, MET, BRCA2, ERBB3, FGFR1, BRAF, and ATM. These findings underscore the critical role of genetic profiling in NECs for guiding personalized therapeutic strategies and highlight the ongoing need for research to further understand the diverse genetic underpinnings and their implications for treatment across different types of NECs.

Our study is subject to several limitations. First, it employs a retrospective analysis approach, which inherently restricts the ability to control for confounders and bias that may influence the outcomes. Importantly, our study also had a limited sample size, which poses challenges in drawing definitive conclusions regarding the efficacy of atezolizumab in a first-line setting. Consequently, further investigations with larger clinical trials are warranted to accurately identify which patient groups might significantly benefit from this regimen. Despite these limitations, we believe our study offers valuable insights into a patient cohort characterized by extremely poor prognosis and limited clinical data, thus providing preliminary data that could inform the further development of systemic therapies.

Conclusion

Our study found that the addition of atezolizumab to EP in the first-line treatment of extrapulmonary NEC did not significantly improve PFS or OS compared with EP alone. Furthermore, an NLR greater than 3 at diagnosis was identified as a poor prognostic marker for OS.

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Author contributions

I-Wei Ho (Conceptualization, Formal analysis, Writing—original draft, Visualization), Nai-Jung Chiang (Supervision, Writing—review & editing), Jiun-I Lai (Supervision, Writing—review & editing), Peter Mu-Hsin Chang (Supervision, Writing—review & editing), San-Chi Chen (Supervision, Writing—review & editing), Yi-Ping Hung (Supervision,

Writing—review & editing), and Ming-Huang Chen (Conceptualization, Data curation, Supervision, Validation, Writing—review & editing, Funding acquisition)

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Conflict of interest

The authors declare no potential conflicts of interest related to the research, authorship, and publication of this manuscript.

Data Availability

The data generated and analyzed in this study are derived from patient records at Taipei Veteran general hospital and are not publicly available due to privacy and ethical restrictions. Access to the data is limited and requires approval from the Institutional Review Board (IRB).

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