Nivolumab ± Ipilimumab in Patients With Pretreated Advanced Neuroendocrine Carcinoma: The GCO-001 NIPINEC Randomized Phase II Trial

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ABSTRACT

PURPOSE There is no standard second-line therapy for gastroenteropancreatic (GEP) and lung large-cell neuroendocrine carcinoma (NEC) after the failure of platinum-based chemotherapy. This study aimed to investigate the efficacy of nivolumab ± ipilimumab.

METHODS The GCO-001-NIPINEC (ClinicalTrials.gov identifier: NCT03591731) trial was a noncomparative, open-label, phase II trial. The main inclusion criteria were age ≥18 years, performance status (PS) ≤2, advanced large- and small-cell GEP-NEC and large-cell lung NEC, and second- or third-line treatment for NECs refractory to platinum-based chemotherapy. Patients were randomly assigned (1:1) and stratified by age and PS to receive nivolumab (3 mg/kg/once every 2 weeks) ± ipilimumab (1 mg/kg/once every 6 weeks) for 2 years or until progression or unacceptable toxicity. The primary end point was objective response rate (ORR) at 8 weeks, assessed by investigators.

RESULTS A total of 185 patients (91 in the nivolumab arm and 94 in the nivolumab-ipilimumab arm) were enrolled between December 2018 and March 2021; 169 were analyzed (median age of 64.5 years, 71% male, 91% PS 0-1). The main primary tumor locations were lungs (50%), colorectal (15%), gastroesophageal (14%), and pancreatic (13%) regions. The ORR at 8 weeks was 7.2% (95% CI, 2.7 to 15.1]) in the nivolumab arm and 14.0% (95% CI, 7.4 to 23.1) in the nivolumab-ipilimumab arm. The best ORR was 9.6% and 20.9%, respectively, whereas the median progression-free and overall survival were approximately 2 months and 6 months in both arms. One treatment-related death occurred, in the nivolumab arm. The grade 3-4 adverse events (≥5%) were asthenia (13%), gamma-glutamyl transferase increase (10%), alkaline phosphatase increase (9%), dyspnea (7%), and anemia (6%) in the nivolumab-ipilimumab arm.

CONCLUSION Nivolumab-ipilimumab could be a second-/third-line treatment option for patients with NECs. However, given the limited magnitude of benefit, studies are warranted to evaluate its use earlier and/or associated with chemotherapy.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Poorly differentiated neuroendocrine carcinomas (NECs) of the lung and the gastroenteropancreatic (GEP) system constitute a distinct family of tumors that share morphologic, immunohistochemical, molecular, clinical, and outcome characteristics.[1] After the failure of platinum-based chemotherapy, there is no standard-of-care for second-line treatment or beyond.[2] Fluorouracil, leucovorin, and irinotecan (FOLFIRI) as well as different types of single-agent chemotherapy (pemetrexed, docetaxel, paclitaxel, gemcitabine-oxaliplatin, or topotecan) could be considered standard second-line treatments in patients with GEP-NEC or lung large-cell (LC) NEC, respectively;

CONTEXT

Key Objective

Is nivolumab ± ipilimumab relevant in second- or third-line refractory to platinum-based chemotherapy in neuroendocrine carcinomas (NECs)?

Knowledge Generated

The primary end point (objective response rate at 8 weeks) was reached in the nivolumab-ipilimumab arm, but not in the nivolumab arm. However, the response duration and overall survival remain low under both immunotherapies alone after first-line chemotherapy in NECs.

Relevance *(E.M. O'Reilly)*

The data from this trial provide modest support for dual immune checkpoint blockade in a subset of individuals with high grade neuroendocrine malignancies.*

*Relevance section written by *JCO* Associate Editor Eileen M. O'Reilly, MD, FASCO.

however, the median OS ranges from 7.0 to 9.0 months in prospective studies, which is disappointing.[3-5]

The use of immune checkpoint inhibitors (ICIs) has changed the treatment paradigm in many cancer types, including some NECs, such as Merkel cell carcinoma[6] and small cell lung cancer over the last decade.[7,8] There are few data on the efficacy of ICIs in the post–first-line treatment of GEP-NEC, and most data have been obtained from small cohorts of basket trials and/or trials, in which differentiations of grade 3 neuroendocrine neoplasms (NENs), well-differentiated grade 3 neuroendocrine tumors (NETs), and NECs were merged. Preliminary data have been disappointing, at least for ICIs given as a monotherapy.[2] In the DUNE trial, the only cohort that met the primary end point (OS rate at 9 months above 23%) was cohort 4, which included 33 patients with GEP-NEN-G3 (18 with NEC and 15 with NET-G3) who were treated with durvalumab and tremelimumab.[9] Moreover, single case studies have reported the efficacy of ICIs in treating lung LC-NECs,[10] together with frequent increases in the expression of PD-L1 in tumors.[11]

Therefore, the present study investigated the contribution of nivolumab ± ipilimumab administered as second-line or third-line treatment for patients with GEP-NEC or lung-NEC after the failure of first-line platinum-etoposide chemotherapy.

METHODS

Study Design and Participants

The GCO-001-NIPINEC (EudraCT 2017-003863-37—ClinicalTrials.gov identifier: NCT03591731) trial was the joint academic effort of three French national oncology groups (IFCT, Fédération Francophone de Cancérologie Digestive [FFCD], and GERCOR). This was a multicenter, noncomparative, open-label, randomized (1:1) phase II trial with a two-step design (early stopping due to futility after 50% accrual) that assessed the safety and efficacy of nivolumab and nivolumab-ipilimumab after platinum-etoposide failure in patients with GEP-NEC or lung LC-NEC.

All the patient eligibility criteria are detailed in the study protocol (Protocol): age ≥18 years; histologically confirmed lung LC-NEC and GEP-NEC (according to the WHO classification[1]); unresectable locally advanced or metastatic disease; disease progression (determined using the RECIST v.1.1 criteria) after one or two previous lines of systemic treatment, including at least one line of platinum-etoposide chemotherapy; measurable disease (RECIST 1.1 criteria); and an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2, which was subsequently amended to a PS <2. A safety analysis was scheduled during the interim analysis, with particular attention given to the patients with a PS of 2; the protocol was therefore amended (August 28, 2020) to include only patients with a PS <2 since the initially included patients with a PS of 2 at baseline had poor outcomes. The exclusion criteria were uncontrolled brain metastases, previous use of ICIs, and usual contraindication of ICIs. A central pathologic review was performed by four expert pathologists.

Random Assignment and Masking

The participants were randomly assigned (1:1) to receive nivolumab or nivolumab-ipilimumab using a minimization method (random factor of 0.8 for improved concealment) designed to minimize imbalance between treatments, taking the following stratification factors into account: a PS of 0/1 versus 2, and an age <70 years versus ≥70 years. The

primary site of the NEC was not a stratification factor. Neither patients nor investigators were masked to group assignment.

Procedures

The patients received intravenous (IV) nivolumab (3 mg/kg) over 30 minutes once every 2 weeks or IV nivolumab (same schedule) and ipilimumab (1 mg/kg) over 30 minutes once every 6 weeks. For both arms, the treatment was given until disease progression, unacceptable toxicity, patient refusal, or a maximum of 2 years. There was no dose reduction for either drug. Dose delays are detailed in the study protocol (pages 33-37). A treatment interruption >6 weeks for nivolumab and >12 weeks for ipilimumab required treatment discontinuation.

Adverse events (AEs) were evaluated during consultations by assessing the general and clinical conditions of the patients and by collecting data on the events occurring between visits; regular blood tests (hematology and blood chemistry) were performed every 14 days (±3 days), before each cycle. Radiologic evaluations using a thoracic-abdominopelvic computed tomography scan and brain imaging for patients with target brain lesions were performed every 8 ± 1 week. Quality of life (QoL) was assessed at weeks 8, 16, 24, 48, 72, and 96 by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) scale.

Outcomes

The primary end point was the proportion of patients with an objective response rate (ORR) assessed 8 weeks after random assignment (defined as the number of patients with an objective response assessed by investigators using the RECIST 1.1 criteria[12]) divided by the number of assigned eligible patients. A post hoc analysis was also performed to describe the primary and secondary end points according to the primary tumor site (GEP and lung).

The secondary end points were the ORR and disease control rate assessed 8 weeks after random assignment by independent central review, the response duration, progression-free survival (PFS) by investigators, OS, the time until definitive deterioration (TUDD), and safety (using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5.0). The best ORR (according to the RECIST v1.1 criteria) was assessed via post hoc analysis. PFS was measured from the date of random assignment to the date of the event, which was defined as the first documented instance of disease progression (by the RECIST v1.1 criteria) or death from any cause, and OS was calculated from the date of random assignment to the date of death. The best ORR and PFS were assessed using investigator evaluation. The response duration was calculated from the date at which the ORR was reported to the first date of documented progressive disease or death. The TUDD was defined as the interval between baseline and a decrease in the QLQ-C30 global score ≥5 points, with no further increase in the QoL score ≥5 points or if patient dropout occurred after this decrease, resulting in missing data. Patients were censored at the last follow-up (or at the end point date if it occurred before the last follow-up) when no decrease in the QoL score compared with baseline was observed or when a decrease was observed but then followed by a significant increase in the QoL score compared with baseline. Patients with a baseline score but no follow-up score were included in the analysis; however, they were censored immediately after the baseline assessment.

Statistical Analysis

We used a test for a single binomial proportion for a two-stage design and the O'Brien-Fleming stopping rules, allowing for early stopping due to futility after stage 1. An ORR at 8 weeks ≤5% was considered unacceptable. The ORR was considered favorable at 8 weeks if it was ≥15% with an α risk value of 5% (two-sided) and a statistical power of 90%. A total of 41 patients were included in the first stage (for each arm). According to the hypothesis, if there were ≤2 responses among these 41 patients, the study would have been stopped due to futility. Otherwise, 40 additional patients were enrolled, for a total of 81 patients in each arm. At the end of step 2, the null hypothesis was rejected if ≥9 responses were obtained from 81 patients. Overall, up to 90 patients were enrolled in each arm to account for possible noneligible patients.

The intention-to-treat (ITT) population included all patients randomly assigned in the study. All patients who received at least one infusion of nivolumab or nivolumab + ipilimumab were included in the safety analysis. The eligible population for the primary end point was defined as all the patients in the ITT population without any major deviation from the inclusion/noninclusion criteria.

The ORR at 8 weeks is provided with its 95% CI, which was calculated by the Clopper-Pearson method for each arm. A Kaplan-Meier analysis was used to estimate the median PFS (mPFS), OS, TUDD, and duration of response for the subgroup of patients who had a response (complete or partial) and the associated 95% CIs for each arm. The median (95% CI) follow-up was calculated using the inverse Kaplan-Meier method. AEs are described by numbers of patients and percentages. A stepwise logistic regression analysis was performed to explore the demographic and clinical factors associated with the ORR, and univariable Cox models were used to determine the putative prognostic variables, including sex (male *v* female), ECOG PS (0-1 *v* 2), age (<70 years *v* ≥70 years), line of treatment (second- *v* third-line treatment), histology (small cell *v* large cell *v* other), primary site (colon *v* lung *v* pancreatobiliary), and Ki67 (≤median *v* >median). A multivariable stepwise Cox model was then used to determine the prognostic value of all the cited variables. *P* values were considered significant at $P < .05$.

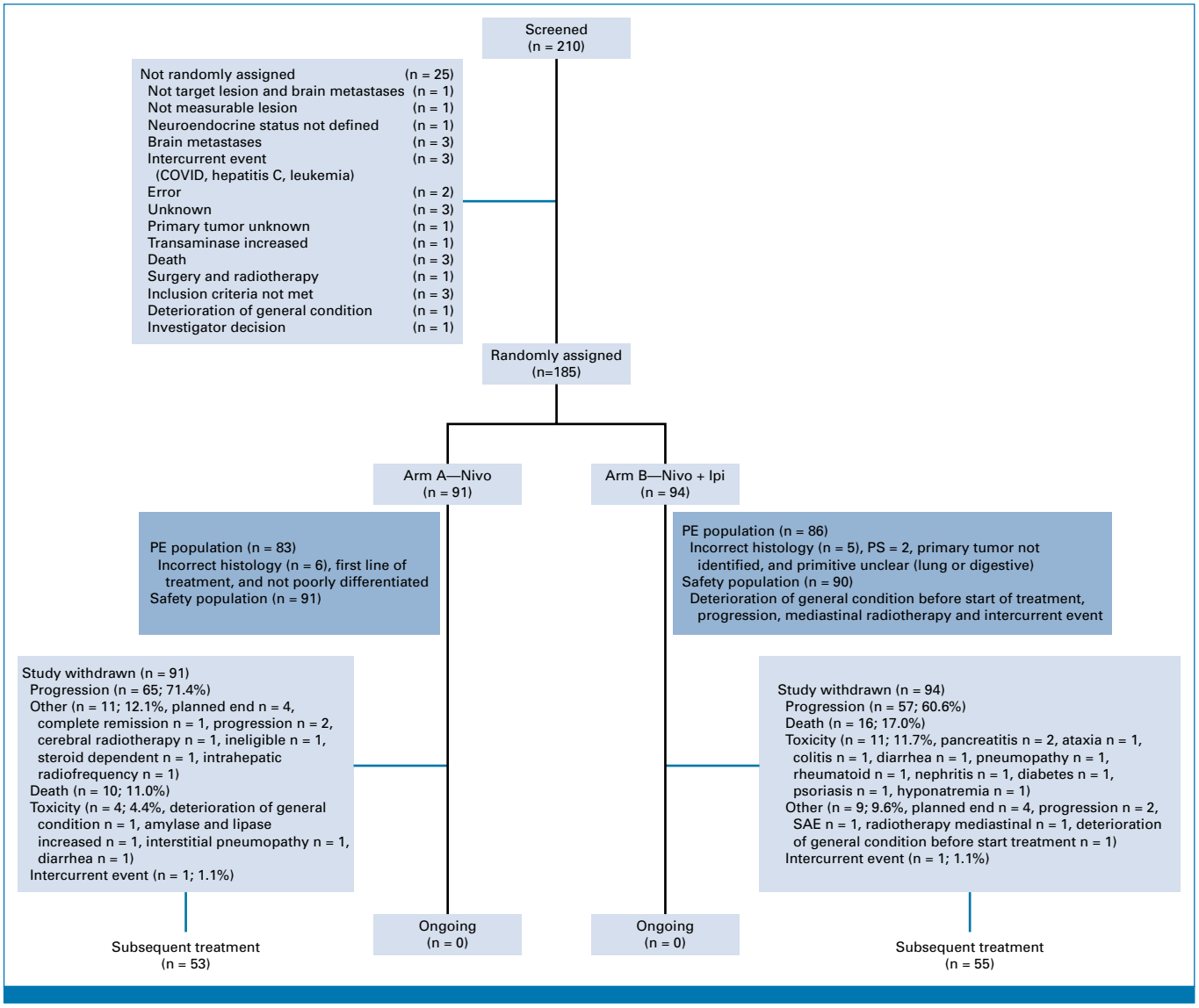

FIG 1. Patient flow chart. PE, eligible population; PS, performance status; SAE, severe adverse event.

The cutoff date for data collection was December 15, 2024. All analyses were performed using SAS software, version 9.4 (SAS Institute).

Ethical Considerations

The study was approved by an institutional review board and complied with the Declaration of Helsinki as well as the principles of good clinical practice guidelines (including written informed consent). Data on race/ethnicity were not collected according to French legislation.

RESULTS

Patients and Treatments

A total of 210 patients were screened in 50 French centers (Data Supplement, Table S1, online only) from December 2018 to March 2021, of whom 185 patients were randomly assigned to the nivolumab (n = 91) arm or nivolumab-ipilimumab (n = 94) arm. Among the 185 randomly assigned patients included in the ITT population, four in the nivolumab-ipilimumab arm did not initiate treatment. Sixteen patients had major deviations from the inclusion criteria (eight in each arm), mainly due to incorrect histology. A total of 169 eligible patients were ultimately analyzed for efficacy outcomes; 83 were treated with nivolumab and 86 were treated with the nivolumab-ipilimumab combination (Fig 1).

In the ITT population, the baseline characteristics were balanced between the two groups (Table 1). The median (IQR) age was 64.5 (57.9-71.7) years, 132 patients (71%) were male, and 168 patients (91%) had a PS of 0 or 1. The main primary tumor locations were the lung (50%), colorectal (15%), gastroesophageal region (14%), and pancreas (13%). The median (IQR) Ki67 index was 80% (60-90) for both

TABLE 1. Patient Characteristics of the Eligible Population (n = 185)

Characteristic	N[a]	Lung		Digestive	
		Nivolumab (n = 45)	Nivolumab-Ipilimumab (n = 48)	Nivolumab (n = 46)	Nivolumab-Ipilimumab (n = 46)
Age, years, median (range)	185	61.6 (38.7-82.2)	65.3 (26.4-84.1)	65.3 (26.6-80.9)	64.9 (27.3-87.1)
Male sex, No. (%)	185	35 (77.8)	29 (60.4)	35 (76.1)	33 (71.7)
Smoker status, No. (%)	183	41 (91.1)	41 (85.4)	21 (47.7)	22 (50)
Performance status, No. (%)	185				
0		18 (40.0)	15 (31.3)	19 (41.3)	9 (19.6)
1		24 (53.3)	29 (60.4)	22 (47.8)	32 (69.6)
2		3 (6.7)	4 (8.3)	5 (10.9)	5 (10.9)
Primary tumor location, No. (%)	169				
Lung		45 (100)	48 (100)	—	—
Colorectal		—	—	13 (28.3)	15 (32.6)
Gastroesophageal		—	—	15 (32.6)	11 (23.9)
Pancreas		—	—	13 (28.3)	11 (23.9)
Biliary tract		—	—	2 (4.3)	3 (6.5)
Other GI[b]		—	—	3 (6.5)	6 (13.0)
WHO classification, No. (%)	169				
Small-cell NEC		0 (0)	0 (0)	8 (17.4)	18 (39.1)
Large-cell NEC		44 (97.8)	48 (100)	16 (34.8)	19 (41.3)
Without specification size NEC		—	—	18 (39.1)	7 (15.2)
Mixed neoplasm with NEC component >70% or other		—	—	4 (8.7)	2 (4.3)
Ki67 index, %, median (range)	158	70.0 (1-100)	80.0 (1-100)	80.0 (25-95)	80.0 (30-98)
Ki67 ≥55%, No. (%)		24 (70.6)	30 (83.3)	36 (80)	35 (81.4)
Prior line of treatment, No. (%)	185				
1		37 (82.2)	38 (79.2)	20 (43.5)	21 (45.7)
2		8 (17.8)	10 (20.8)	26 (56.5)	25 (54.3)
PDL-1 status ≥1%, n/N (%)	65	13/28 (46.4)	9/26 (34.6)	4/6 (66.7)	3/5 (60.0)
PDL-1 status centralized ≥1%, n/N (%)	144	3/38 (7.9)	6/36 (16.7)	3/33 (9.1)	1/37 (2.7)

Abbreviation: NEC, neuroendocrine carcinoma.
[a]Patients with available data.
[b]Liver (n = 5), coeliomesenteric (n = 1), duodenum (n = 1), ileum (n = 1), anal canal (n = 1).

groups. A total of 157 (85%) patients had ≥2 metastatic sites, with metastases located in the liver in 116 (63%) patients, in intra-abdominal lymph nodes in 52 (28%) patients, and in the mediastinum in 52 (28%) patients. The majority of patients received immunotherapy as second-line treatment following platinum-etoposide chemotherapy.

The median (IQR) number of cycles of nivolumab was 4 (2-10) in the nivolumab arm; for the nivolumab-ipilimumab arm, the median (IQR) number of cycles was 4 (2-11) for nivolumab and 2 (1-4) for ipilimumab (Data Supplement, Table S2). The median (IQR) nivolumab duration was 1.4 (0.5-4.2) months in the nivolumab arm and 1.4 (0.5-4.9) months in the nivolumab-ipilimumab arm. The reasons for treatment discontinuation in the nivolumab arm and nivolumab + ipilimumab arm were disease progression (71% and 63%), death (11% and 18%), toxicity (4% and 12%), intercurrent events (1% and 0%), and other reasons (12% and 7%). A total of 108 (58%) patients received subsequent systemic treatment after disease progression: 53 (58%) in the nivolumab arm and 55 (59%) in the nivolumab-ipilimumab arm (Data Supplement, Table S3).

Efficacy

The ORR, assessed by investigators (primary end point) 8 weeks after random assignment, was 6/83 (7.2% [95% CI, 2.7 to 15.1]) in the nivolumab arm and 12/86 (14.0% [95% CI, 7.4 to 23.1]) in the nivolumab-ipilimumab arm (Table 2). Among the 44 patients who presented with lung primary tumors and were treated with nivolumab-ipilimumab, eight (18.2%) had an ORR assessed at 8 weeks. The ORR at 8 weeks, as assessed by independent central review, was 5 (7% [95% CI, 1.1 to 13.0]) in the nivolumab arm and 8 (11.8% [95% CI, 4.1 to 19.4]) in the nivolumab-ipilimumab arm. The disease control rate at 8 weeks was 32/83 (38.6% [95% CI, 28.1 to

TABLE 2. Morphologic Response in the Eligible Population (n = 169) According to the Treatment Arm

	All		Lung		Digestive	
Morphological Response Criteria	N (n = 83)	N-I (n = 86)	N (n = 41)	N-I (n = 44)	N (n = 42)	N-I (n = 42)
Morphologic response at 8 weeks, No. (%)						
Objective response	6 (7.2)	12 (14.0)	3 (7.3)	8 (18.2)	3 (7.1)	4 (9.5)
Stable disease	26 (31.3)	15 (17.4)	17 (41.5)	9 (20.5)	9 (21.4)	6 (14.3)
Progressive disease	42 (50.6)	46 (53.5)	17 (41.5)	21 (47.7)	25 (59.5)	25 (59.5)
Not evaluable/missing	9 (10.8)	13 (15.1)	4 (9.8)	6 (13.6)	5 (11.9)	7 (16.7)
Best objective response, No. (%)	8 (9.6)	18 (20.9)	5 (12.2)	12 (27.3)	3 (7.1)	6 (14.3)
Response duration, months, median (IC 95%)	12.2 (1.9 to NR)	12.0 (5.6 to 30.0)	5.4 (1.9 to NR)	8.5 (3.1 to 25.4)	NR (3.7 to NR)	22.3 (3.3 to NR)

Abbreviations: N, nivolumab; N-I, nivolumab-ipilimumab; NR, not reached; PS, performance status.

49.9]) in the nivolumab arm and 27/86 (31.4% [95% CI, 21.8 to 42.3]) in the nivolumab-ipilimumab arm.

The best ORR (by investigators) was observed in eight (9.6% [95% CI, 4.3 to 18.1]) of 83 patients in the nivolumab arm and 18 (20.9% [95% CI, 12.9 to 31.0]) of 86 patients in the nivolumab-ipilimumab arm. The median (95% CI) duration of response was 12.2 (95% CI, 1.9 to not reached [NR]) months in the nivolumab arm and 12.0 (95% CI, 5.6 to 30.0) months in the nivolumab-ipilimumab arm (Table 2). In the multivariable analysis of the demographic and clinical factors associated with the best ORR, only female sex was associated with a greater best ORR (OR, 9.8 [95% CI, 1.3 to 76.9]; P = .03; Data Supplement, Table S4). Among the 26 patients with an ORR, nine had a GEP origin. Of them, eight had enough tumor specimen available, and all these patients had a proficient mismatch repair (MMR) status.

After a median (95% CIs) follow-up of 53.5 (95% CI, 46.6 to 69.1) months, the mPFS (95% CI (by investigators) was 1.8 (95% CI, 1.7 to 2.0) months in the nivolumab arm and 1.9 (95% CI, 1.6 to 2.0) months in the nivolumab-ipilimumab arm. At the cutoff date for data collection, 154 (91%) of 169 patients had died. The median (95% CI) OS was 6.2 (95% CI, 3.7 to 9.4) months in the nivolumab arm and 6.1 (95% CI, 3.5 to 7.8) months in the nivolumab-ipilimumab arm. The 6- and 12-month OS rates were 50.6% (95% CI, 39.4 to 60.7) and 33.7% (95% CI, 23.8 to 43.9) in the nivolumab arm and 50.0% (95% CI, 39.1 to 60.0) and 32.6% (95% CI, 23.0 to 42.5) in the nivolumab-ipilimumab arm, respectively. The median OS times were 10.2 (95% CI, 4.9 to 19.4) and 9.8 (95% CI, 4.6 to 18.4) months for the patients with lung LC-NEC and 3.7 (95% CI, 2.2 to 7.1) and 3.3 (95% CI, 2.0 to 5.6) months for the patients with GEP-NEC in the nivolumab and nivolumab-ipilimumab arm, respectively (Fig 2).

Safety and QoL

One treatment-related death occurred in the nivolumab arm (due to encephalitis); no treatment-related death occurred in the nivolumab-ipilimumab group. All other deaths were not related to treatment. Treatment-related AEs led to discontinuation in four (4.4%) patients receiving nivolumab and 11 (12.7%) patients receiving nivolumab-ipilimumab. Overall, grade 3-5 treatment-related AEs were observed in 14 (15%) patients in the nivolumab arm and 21 (23%) patients in the nivolumab-ipilimumab arm. The grade 3-4 AEs (≥5%) were asthenia (13%), gamma-glutamyltransferase increase (10%), alkaline phosphatase increase (9%), dyspnea (7%), and anemia (6%) in the nivolumab-ipilimumab arm and anemia (7%), abdominal pain (7%), and asthenia (5%) in the nivolumab arm (Fig 3). The AEs are detailed in the Data Supplement (Table S5).

The TUDD was 4.0 (95% CI, 2.3 to 11.6) months in the nivolumab arm and 5.6 (95% CI, 2.2 to NR) months in the nivolumab-ipilimumab arm (Data Supplement, Fig S1).

DISCUSSION

In this large randomized phase II trial focusing on lung LC-NEC and GEP-NEC, the primary end point was reached for the combination of nivolumab-ipilimumab, but not for single-agent nivolumab. The ORR at 8 weeks was greater, reaching 18.2%, in patients with lung LC-NEC who were treated with nivolumab-ipilimumab. However, the majority of patients had progressive disease at their first evaluation, and the response duration and the PFS/OS were not very different between arms.

The efficacy of single-agent anti–PD-L1/PD-1 therapy, such as nivolumab, is limited in a population of patients with unselected NEC. The results of the present study are concordant with the ORRs (best ORR herein) below 10% reported in smaller studies of spartalizumab,[13] avelumab,[14] or pembrolizumab.[15] In contrast, combining anti–PD-L1/PD-1 therapy with anti–cytotoxic T-cell lymphocyte-4 therapy seems to be more effective. Nivolumab-ipilimumab was associated with an ORR of 21% in the present study and an ORR of 26% in the DART-SWOG trial (which included a mix of 19 patients with both NEC and NET-G3).[16] In cohort 4 of the DUNE trial, the ORR was 9.1% in 33 patients with GEP-NEN-G3 (including 18 with NEC) treated using durvalumab-tremelimumab, and this was the only cohort with a positive

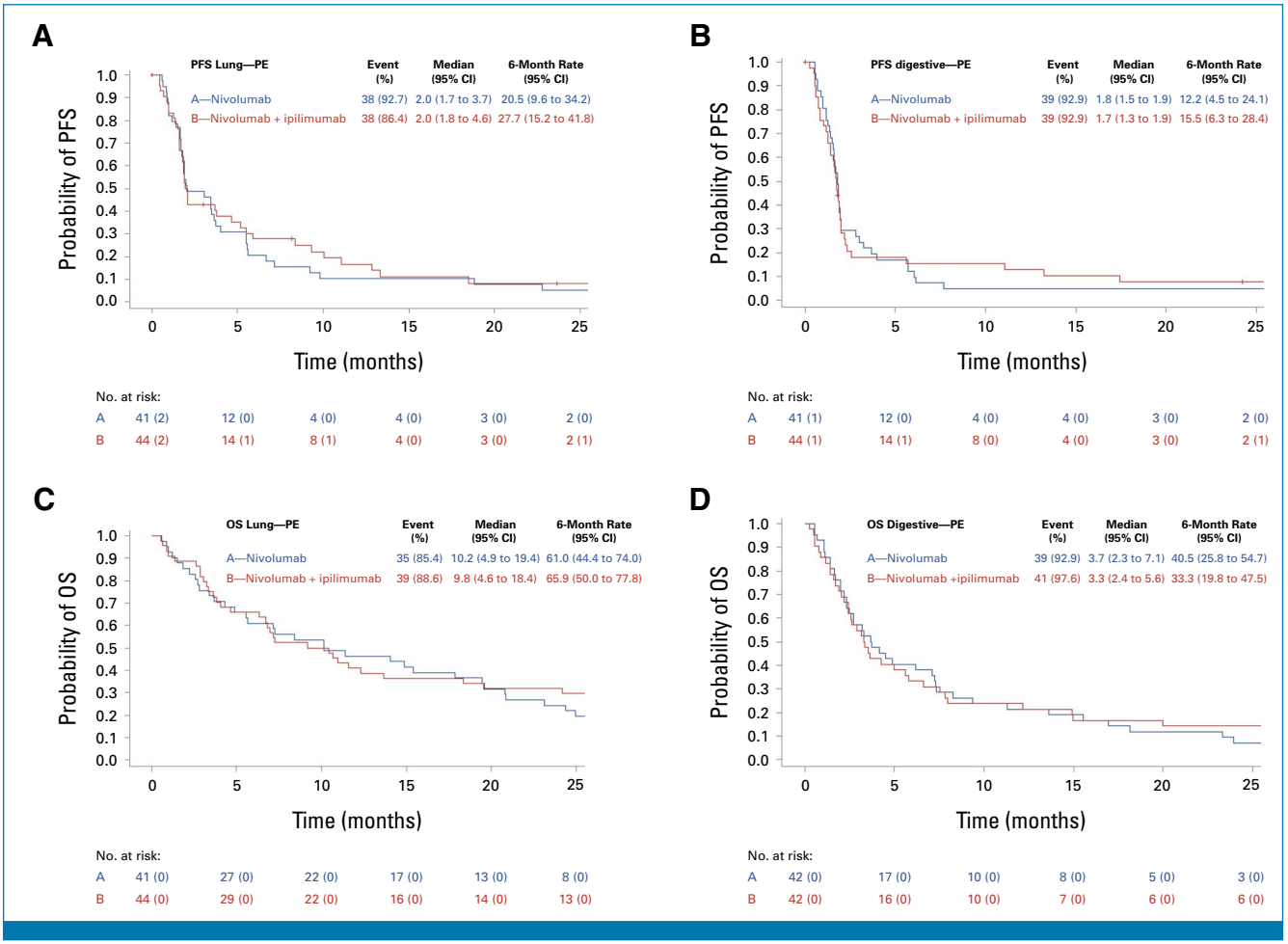

FIG 2. PFS and OS in patients with lung (A, C) and digestive (B, D) NECs according to treatment arm (A: nivolumab, B: nivolumab-ipilimumab) in the eligible population. NEC, neuroendocrine carcinoma; OS, overall survival; PE, eligible population; PFS, progression-free survival.

result for the primary end point, which was OS at 9 months (36.1%).[9] In patients with lung LC-NEC, a 27% ORR, with potentially prolonged responses in responders, is highly valuable in clinical practice given the poor efficacy of all second-line options. However, the ORR under dual immunotherapy remains too low in patients with GEP-NECs, to be used outside of clinical trials. Herein, the mPFS is directly linked to the frequency of imaging since many patients had experienced disease progression at their first evaluation, which was performed every 12 weeks in the DUNE trial (mPFS was 2.4 months with durvalumab-tremelimumab)[9] and every 8 weeks in the present study (mPFS was 1.9 months with nivolumab-ipilimumab). In addition, the 6- or 12-month OS is more pertinent for the evaluation of treatment efficacy in NEC. The 12-month OS was 33% in the present study of nivolumab-ipilimumab and 30% in the DART trial[16] and in cohort 4 of the DUNE trial.[9]

To improve the outcomes of patients with NEC, an anti–PD-1 agent was combined with chemotherapy[17] or a tyrosine kinase inhibitor, such as surufatinib.[18] These combinations are being evaluated in ongoing randomized comparative studies: surufatinib-toripalimab versus FOLFIRI (ClinicalTrials.gov identifier: NCT05015621) and FOLFIRI in association with dual immunotherapy (zimberelimab-domvanalimab) versus FOLFIRI in the REWENEC-01 study.[20] In addition, the search for predictive factors of response, such as a deficient (d) MMR status or high tumor mutation burden, is important since pembrolizumab is approved to be used through an agnostic approach, regardless of the histologic type. Interestingly, although the frequency of dMMR GEP-NEC in the present study was unknown, all patients who achieved an ORR had a proficient MMR GEP-NEC, highlighting that some additional patients outside of dMMR may respond. Another interesting type of immunotherapy is to target Delta-like ligand 3. Indeed, DLL3-targeted agents also include bispecific T-cell engagers such as tarlatamab or obrixtamig, which have high efficacy in treating lung NEC.[21,22] Ultimately, precision medicine is also an interesting approach for the few patients with NEC harboring a targetable molecular alteration, such as *BRAF*^{V600E}-mutated NEC, which could be targeted using BRAF ± MEK inhibitors. These molecular alterations seem to be more common in patient with right-sided colon NEC.[23]

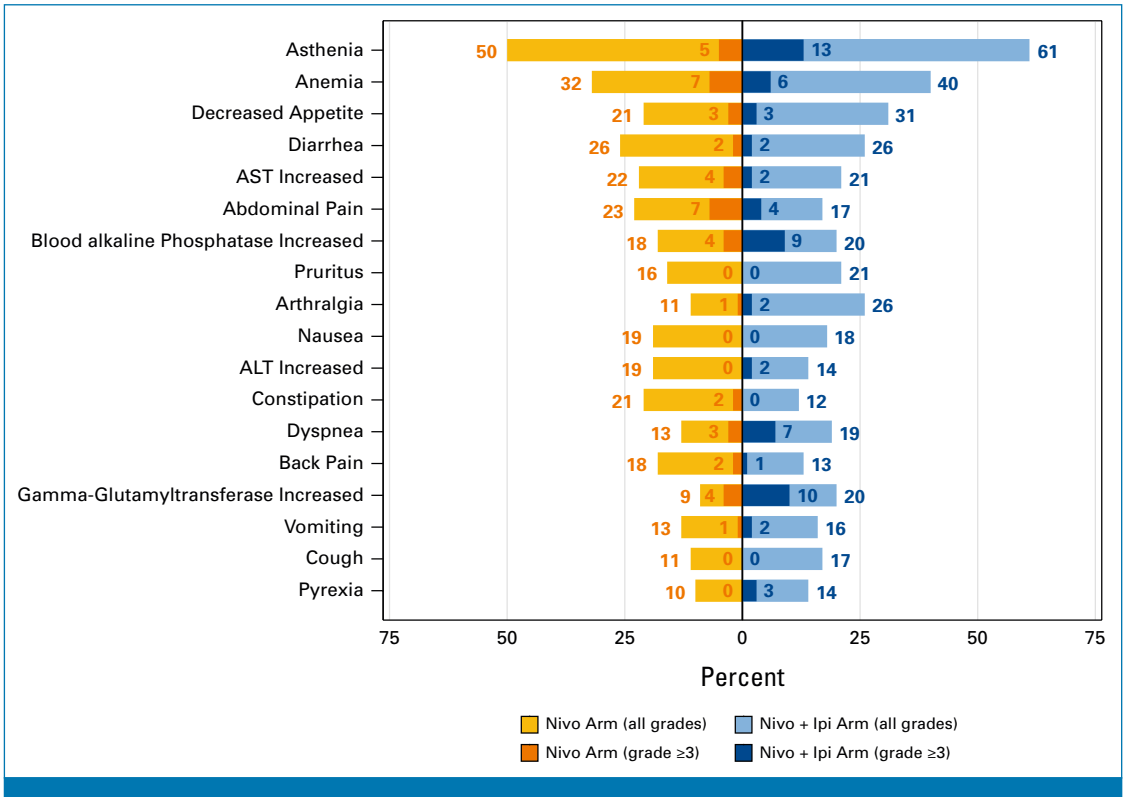

FIG 3. Most frequent AEs according to the treatment arm and the grade of toxicity (G1/2 and ≥ G3). AE, adverse event.

The present study has several strengths, as it included a relatively large patient numbers for such rare diseases, two homogeneous patient populations (large-cell lung NEC and GEP-NEC, excluding grade 3 NEN but with a well-differentiated morphology), a centralized pathologic review, and a randomized design. In addition, patients with an ECOG PS of 2 were no more included after the scheduled intermediate safety analysis. There are, however, several limitations, including the inability to identify subgroups of patients with high/limited benefits and the enrollment of patients with limited expected survival. In addition, GEP-NEC and lung LC-NEC are quite heterogeneous in terms of molecular aspects and risk factors. Although lung NENs (NEC but also atypical carcinoids treated by spartalizumab in another study)[13] seemed to respond better to immunotherapy than GEP-NECs, the primary site was not a stratification factor. Fortunately, there was no imbalance in the included population regarding this important factor. Further studies are warranted to evaluate immunotherapy, potentially in combination with other treatments, in lung NENs rather than in GEP-NECs, and earlier during the treatment course such as in the neoadjuvant or adjuvant setting. In addition, the ORR was chosen as the primary end point, rather than PFS/OS, which is often performed in clinical trial development. Nevertheless, OS could be a better and a less biased primary end point in a disease leading to a bad outcome. Based on the analogy with other cancer, a minimum of 15% on ORR was judged necessary to go for further development of immunotherapy alone in NEC. Finally, an important limitation was the absence of central review for best ORR and PFS; in addition, there was a discrepancy between local and central review, and not all images were available to be reviewed. Therefore, even in the nivolumab-ipilimumab arm, only eight patients had ORR at 8 weeks according to central review (just below the cutoff to reject the null hypothesis).

In conclusion, although the primary end point of the present study was met, dual immunotherapy did not seem to provide sufficient efficacy. Further studies combining dual immunotherapy with chemotherapy are ongoing in patients with GEP-NEC.

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DATA SHARING STATEMENT

Researchers with appropriate proposals can request deidentified individual participant data. The full details of the protocol and the statistical analysis plan are available in Supplementary data. Data collected for the study, including participant data with identifiers and a data dictionary defining each field in the set, are not available. The data will be shared after the approval of a proposal, with a signed data access agreement.

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Nivolumab ± Ipilimumab in Patients With Pretreated Advanced Neuroendocrine Carcinoma: The GCO-001 NIPINEC Randomized Phase II Trial

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