Clinical Study Report

[A PHASE II STUDY OF DURVALUMAB (MEDI4736) PLUS TREMELIMUMAB FOR THE TREATMENT OF PATIENTS WITH ADVANCED NEUROENDOCRINE NEOPLASMS OF GASTROENTEROPANCREATIC OR LUNG ORIGIN (THE DUNE TRIAL)]

[ESR 15-11561-61-DUNE]

[December13th 2022]

CONFIDENTIAL

Name of Sponsor: Spanish Group of Neuroendocrine and Endocrine Tumors (GETNE)	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use Only)**
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Name of Active Ingredient: 1-Durvalumab 2-Tremelimumab		

Signature pages for clinical study report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Coordinating Investigator:

Signed:  Date: __20__/__12__/___2022___

Print name: Dr. Jaume Capdevila

Affiliation: Vall d'Hebron University Hospital

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Sponsor representative:

Signed:  Date: _20___/_12___/___2022___

Print name: Dr. Jaume Capdevila

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1 TITLE PAGE

Study title: A phase II study of durvalumab (MEDI4736) plus tremelimumab for the treatment of patients with advanced neuroendocrine neoplasms of gastroenteropancreatic or lung origin (the dune trial)

Name of Test Drugs:

1- Durvalumab (IMFINZI)

ATC code: Antineoplastic agents, monoclonal antibodies L01FF03

2-Tremelimumab

ATC code: None

Indication studied: Patients with advanced/metastatic, histologically confirmed, grade 1/2 (G1/G2) of the 2010 WHO classification neuroendocrine tumors of the pancreas, gastrointestinal tract and lung origins and grade 3 (G3) of gastroenteropancreatic system or unknown primary site (excluding lung primaries) after progression to previous therapies.

Study description: The DUNE trial was a prospective, multi-center, open label, stratified, exploratory, phase II study evaluating the efficacy and safety of durvalumab plus tremelimumab in different cohorts of patients with neuroendocrine neoplasms. After informed consent was obtained, subjects were screened to assess eligibility criteria and were included in four different cohorts:

- Cohort 1: Well-moderately differentiated lung neuroendocrine tumors (classically known as typical and atypical carcinoids) after progression to somatostatin analogs and one prior targeted therapy or chemotherapy.
- Cohort 2: G1/G2 (WHO grade 1 and 2) gastrointestinal neuroendocrine tumors after progression to somatostatin analogs and one prior targeted therapy.

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- Cohort 3: G1/G2 (WHO grade 1 and 2) pancreatic neuroendocrine tumors after progression to standard therapies (chemotherapy, somatostatin analogs and target therapy), who had received between two and four prior lines of treatment.
- Cohort 4: Neuroendocrine neoplasms (WHO grade 3) of gastroenteropancreatic origin or unknown primary site (excluding lung primary tumors) patients were treated in the second line only, after progression to first-line chemotherapy with a platinum based regimen.

Upon meeting eligibility criteria, eligible subjects received treatment. Patients received 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continued 1500 mg durvalumab q4w starting on Week 16 for up to 8 months (9 doses). Dosing outside the window was discussed with the Study Physician. Tremelimumab was administered first. Durvalumab infusion was started approximately 1 hour after the end of tremelimumab infusion. The duration was approximately 1 hour for each infusion. A 1-hour observation period was required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions were observed during or after the first cycle, subsequent infusion observation periods could be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

Primary endpoint for cohorts 1, 2 and 3:

Nine-months clinical benefit rate (CBR) by Response Evaluation Criteria In Solid Tumors (RECIST 1.1), which was defined as the percentage of patients achieving complete response (CR), partial response (PR), or stable disease (SD) at month 9 after durvalumab plus tremelimumab was started.

Primary endpoint for cohort 4:

Nine-months overall survival rate, which was defined as the percentage of patients alive at month 9 after durvalumab plus tremelimumab was started.

Sponsors: Spanish Group of Neuroendocrine and Endocrine Tumors (GETNE)

Protocol: ESR 15-11561-61-DUNE

Clinical Phase: Prospective/exploratory phase II

Study dates:
Study approval: 02/03/2017
Study initiation: 11/04/2017

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First patient in: 12/04/2017
Database closure: 22/01/2021 Esta es la fecha en la que se realizó el corte de datos siguiendo el informe estadístico

Investigators:

Dr. Jaume Capdevila
Dra. Teresa Alonso Gordoa (Dr. Enrique Grande former IP)
Dr. Alexandre Teulé Vega (Dr. Ramon Salazar former IP)
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Medical Officer: Dr. Jaume Capdevila

Sponsor signatory: Dr. Jaume Capdevila

GCP Statement: This study was performed in compliance with ICH Good Clinical Practise (GCP) including the archiving of essential documents

Date of report: December 13th, 2022

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SYNOPSIS

Title of Study	A phase II study of durvalumab (MEDI4736) plus tremelimumab for the treatment of patients with advanced neuroendocrine neoplasms of gastroenteropancreatic or lung origin (the DUNE trial).
Investigator(s)	

SITE	INVESTIGATOR
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H.U. Ramón y Cajal	Dra. Teresa Alonso Gordoa (Dr. Enrique Grande former IP)
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H.U. La Paz	Dra. Ana Belén Custodio Carretero
H.U. Central de Asturias	Dra. Paula Jiménez Fonseca
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	Complejo Hospitalario de Navarra — Dra. Ruth Vera García (Dr. Antonio Viudez former IP) H.U. Virgen de las Nieves — Dra. Encarnación González Flores H.U. Miguel Servet — Dr. Vicente Alonso Orduña H. Germans Trias i Pujol- ICO Badalona — Dr. José Luis Manzano Mozo H.U. Virgen del Rocío — Dra. Marta Benavent Viñuales H.U. i Politècnic La Fe — Dr. Ángel Segura Huerta H. U. de Donostia — Dra. Adelaida La Casta Muñoa
Study centre(s)	A total of 20 sites in Spain were opened for recruitment. Please see the investigators section above.
Publication	During the development of the clinical trial, 6 submissions were made to international congresses and the manuscript is currently being prepared. List of previous publications: 2017 ASCO Annual Meeting I: Abstract TPS4146. Poster session https://meetinglibrary.asco.org/record/152659/poster Ignacio Matos, Enrique Grande, Rocío García-Carbonero, Carlos Lopez, Alexandre Teulé, Jaume Capdevila..A multicohort phase II study of durvalumab plus tremelimumab for the treatment of patients (PTS) with advanced neuroendocrine neoplasms (NENs) of gastroenteropancreatic (GEP) or lung origin (the DUNE trial-GETNE1601-). J Clin Oncol 35, 2017 (suppl; abstr TPS4146): 10.1200/JCO.2017.35.15_suppl.TPS4146. 15th Annual ENETS Conference (2018): Abstract #2068. Poster https://www.enets.org/abstract/durvalumab-plus-tremelimumab-for-the-treatment-of-patients-pts-with-advanced-neuroendocrine-neoplasms-nens-of-lung-or-gastroenteropancreatic-gep-origin-a-phase-ii-multicohort-trial-dune-trial-getne-1601.html Hernando-Cubero J, Manzano J, Benavent M, Lopez C, Teulé R. Durvalumab plus Tremelimumab for the Treatment of Patients (pts) with Advanced Neuroendocrine Neoplasms (NENs) of Lung or Gastroenteropancreatic (GEP) Origin. A Phase II Multicohort Trial (DUNE Trial / GETNE 1601).

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	ESMO Virtual Congress 2020: Abstract 1157O. Proffered Paper session https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/a-multi-cohort-phase-ii-study-of-durvalumab-plus-tremelimumab-for-the-treatment-of-patients-pts-with-advanced-neuroendocrine-neoplasms-nens-of J. Capdevila, A. Teule, C. López, R. García-Carbonero, M. Benavent, A. Custodio, A. Cubillo, V. Alonso, T. Alonso Gordoa, A. Carmona-Bayonas, G. Crespo, M. Blanco-Codesido, P. Jimenez-Fonseca, A. Viúdez, A. La Casta Muñoa, I. Sevilla, M. Llanos, A. Segura, J. Hernando-Cubero, J.L. Manzano. A multi-cohort phase II study of durvalumab plus tremelimumab for the treatment of patients (pts) with advanced neuroendocrine neoplasms (NENs) of gastroenteropancreatic or lung origin: The DUNE trial (GETNE 1601). Annals of Oncology (2020) 31 (suppl_4): S711-S724. 10.1016/annonc/annonc281. ESMO Congress 2021: Abstract 1107P ePoster Display session https://oncologypro.esmo.org/meeting-resources/esmo-congress/durvalumab-plus-tremelimumab-in-patients-with-grade-3-neuroendocrine-neoplasms-of-gastroenteropancreatic-origin-updated-results-from-the-multicent J. Capdevila, S. Landolfi, J. Hernando, A. Teule, R. Garcia-Carbonero, A. Custodio, A. Cubillo, T. Alonso-Gordoa, A. Carmona-Bayonas, G. Crespo, M. Blanco, A. Viudez, A. La Casta, I. Sevilla, Á. Segura, C. López, M. Benavent Viñuales, P. Nuciforo, J.L. Manzano.Durvalumab plus tremelimumab in patients with grade 3 neuroendocrine neoplasms of gastroenteropancreatic origin: Updated results from the multicenter phase II DUNE trial (GETNE 1601). Annals of Oncology (2021) 32 (suppl_5): S906-S920. 10.1016/annonc/annonc678. ESMO Congress 2021: Abstract 1099MO (Mini oral session) https://oncologypro.esmo.org/meeting-resources/esmo-congress/durvalumab-plus-tremelimumab-influence-on-response-to-subsequent-treatments-in-patients-with-neuroendocrine-neoplasms-nens-of-gastroenteropancrea J. Hernando, J.L. Manzano, A. Teule, C. López, R. Garcia-Carbonero, M. Benavent Viñuales, A. Custodio, A. Cubillo, V. Alonso, T. Alonso-Gordoa, A. Carmona-Bayonas, G. Crespo, M. Blanco, P. Jimenez-Fonseca, A. Viudez, A. La Casta, I. Sevilla, M. Llanos, Á. Segura, J. Capdevila. Durvalumab plus tremelimumab influence on response to subsequent treatments in patients with neuroendocrine neoplasms (NENs) of gastroenteropancreatic and lung origins: Results from the phase II DUNE trial (GETNE 1601). Annals of Oncology (2021) 32 (suppl_5): S906-S920. 10.1016/annonc/annonc678. The 19th Annual ENETS Conference (2022): Abstract #3391 (poster presentation)

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	Jaume Capdevila, Alexandre Teule, Jorge Hernando, Carlos López,Rocio Garcia-Carbonero, Marta Benavent Viñuales, Ana Custodio, Antonio Cubillo, Vicente Alonso, Stefania Landolfi, Alejandro Garcia-Alvarez, Jose Luis Manzano.Final results from the DUNE trial (GETNE 1601): durvalumab plus tremelimumab for the treatment of advanced neuroendocrine neoplasms (NENs) of gastroenteropancreatic and lung origins.	
Study period	The study was initiated in 2017 and the close of the database was done in 2021. The study overall duration period was 4 years	**Phase of development:** Prospective, exploratory, Phase II
Date of first enrolment	12/04/2017	
Date of last completed	22/01/2021	
Objectives	<u>Primary Objective</u> -Primary endpoint for cohorts 1, 2 and 3: Nine-months clinical benefit rate (CBR) by Response Evaluation Criteria In Solid Tumors (RECIST 1.1), which was defined as the percentage of patients achieving complete response (CR), partial response (PR), or stable disease (SD) at month 9 after durvalumab plus tremelimumab was started. -Primary endpoint for cohort 4: Nine-months overall survival rate, which was defined as the percentage of patients alive at month 9 after durvalumab plus tremelimumab was started. <u>Secondary Objective</u> -Overall response rate (ORR) by irRECIST. -To assess the duration of response according to irRECIST.	

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	-To assess the median progression-free survival time (PFS) according to irRECIST. -To assess the safety profile of Durvalumab and Tremelimumab in subjects with advanced neuroendocrine neoplasms. -To assess the median overall survival (OS) time. -To assess response status according to irRECIST at 6, 9 and 12 months after the start of study treatment. <u>Exploratory Objective(s)</u> -To evaluate biochemical response (changes in CgA and NSE levels) and its association with response rate and progression-free survival. -To assess whether baseline tumor and blood biomarkers could be predictive of response to durvalumab and tremelimumab therapy. -To explore additional hypotheses related to biomarkers and relationship to durvalumab and tremelimumab efficacy and/or toxicity and neuroendocrine tumors evolution that could have arisen from internal or external research activities.
Methodology	This was a prospective, multi-center, open label, stratified, exploratory, phase II study evaluating the efficacy and safety of durvalumab plus tremelimumab in different cohorts of patients with neuroendocrine neoplasms. After informed consent was obtained, subjects were screened to assess eligibility criteria. Upon meeting criteria, eligible subjects received treatment. The primary efficacy analysis was performed using the binomial test procedure. Secondary endpoints were summarized with descriptive statistics. Continuous variables were summarized with n, mean, standard deviation, and range, frequency counts and percentage of subjects within each category were provided for categorical data. Multivariate regression models were used to study relations between explanatory variables and primary endpoint. Survival analysis was performed to analyze PFS, Kaplan-Meier curves were presented and possible comparisons were tested using the log-rank test or the Cox proportional hazard model for multivariate analysis, hazard ratios (HR) and their 95% confidence interval (CI95%) were provided. Patients with loss of follow-up or treatment discontinuation were included in the final analysis of the primary endpoint if they have at least one tumor evaluation and were considered as

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	censored data for survival endpoints. R software version 3.2.1 and SPSS (BM SPSS Statistics Version 26, Armonk, NY) was used for analyses. Data has been considered from the first patient's inclusion until the close of the database (22 Jan 2021). Safety was assessed on the safety analysis set that included all patients who received at least one dose of durvalumab or tremelimumab. Safety was based on the assessment of adverse events (AEs), clinical laboratory test results, vital signs, and physical examinations.
Number of patients	Planned: At least 126 patients; 31 patients in each cohort 1, 2 and 3 and 33 patients in cohort 4. Analyzed: 150 patients were registered, 23 were excluded for screening failure, 3 patients retreated once, one patient retreated twice, with a total of 123 patients who were considered evaluable; 27 patients (Cohort 1), 31 patients (Cohort 2), 32 patients (Cohort 3) and 33 patients (Cohort 4).
Diagnosis and main criteria for inclusion	<u>Key Inclusion criteria:</u> For inclusion in the study, patients were required to fulfill the following criteria: 1) Written informed consent obtained from the subject prior to performing any protocol-related procedures. 2) Age >18 years at time of study entry. 3) Subjects had histologically confirmed diagnosis of one of the following advanced/metastatic neuroendocrine tumor types: a) **Cohort 1**: Well-moderately differentiated neuroendocrine tumors of the lung (mitotic count ≤10 mitoses x 10 HPF), also known as typical and atypical lung carcinoids, that had progressed to prior somatostatin analog therapy and/or one prior targeted therapy or chemotherapy (only one prior systemic therapy, with the exception of patients that had been treated with somatostatin analogues and other systemic treatment, when two prior treatments were allowed). b) **Cohort 2**: Well-moderately differentiated G1/G2 (WHO grade 1 and 2) gastrointestinal neuroendocrine tumors after progression to somatostatin analogs and one targeted therapy (prior targeted therapy

could be everolimus or a multikinase inhibitor). Prior therapies with interferon alpha-2b or radionucleotide therapy were allowed.

c) **Cohort 3**: Well-moderately differentiated neuroendocrine tumors G1/G2 (WHO grade 1 and 2) from pancreatic origin after progression to standard therapies (chemotherapy, somatostatin analogs and target therapy); patients treated with at least two prior systemic treatment lines and a maximum of four previous treatment lines.

d) **Cohort 4**: Neuroendocrine neoplasms (WHO grade 3) of gastroenteropancreatic origin or unknown primary site (excluding lung primary tumors), patients were treated in the second line only, after progression to first-line chemotherapy with a platinum based regimen.

4. For patients included in cohorts 1, 2 and 3: WHO Classification G1/G2 (mitotic count ≤10 mitoses x 10 HPF) lung typical and atypical carcinoids for cohort 1, G1/G2 (Ki67 ≤ 20% or mitotic count ≤ 20 mitoses x 10 HPF) gastrointestinal for cohort 2 (including stomach, small intestine and colorectal origins), G1/G2 (Ki67 ≤ 20% or mitotic count ≤ 20 mitoses x 10 HPF) pancreatic for cohort 3.

5. For patients included in cohort 4: WHO classification G3 (Ki67>20% or mitotic count >20 mitoses x 10 HPF) gastroenteropancreatic neuroendocrine carcinomas (NEC) or liver metastases of G3 NEC of unknown primary site.

6. Subjects had evidence of measurable disease meeting the following criteria:

a) In case of more than one target lesion, it could be identified at least 1 lesion of ≥ 1.0 cm in the longest diameter for a non lymph node, or ≥ 1.5 cm in the short-axis diameter for a lymph node, which was serially measurable according to RECIST 1.1 using computerized tomography/magnetic resonance imaging (CT/MRI). If there was only one target lesion and it was a non-lymph node, it had a longest diameter of ≥ 1.5 cm.

b) Lesions that had external beam radiotherapy (EBRT) or loco-regional therapies such as radiofrequency (RF) ablation or liver embolization showed evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.

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	c) Subjects showed evidence of disease progression by radiologic image techniques within 12 months (an additional month was allowed to accommodate actual dates of performance of scans, i.e., within ≤ 13 months) prior to signing informed consent, according to RECIST 1.1. 7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 8. Life expectancy of at least 12 weeks. 9. Adequate normal organ and marrow function as defined below: ▪ Haemoglobin ≥ 9.0 g/dL. ▪ Absolute neutrophil count (ANC) ≥ 1.5 x 10 9 /L (> 1500 per mm^3). ▪ Platelet count ≥ 100 x 10^9/L (> 100,000 per mm^3). 10. Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This did not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that was predominantly unconjugated in the absence of hemolysis or hepatic pathology), who were allowed only in consultation with their physician. 11. AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases were present, in which case it was ≤ 5x ULN. 12. Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance: Males: Creatinine CL (mL/min) = Weight (kg) x (140 – Age) / 72 x serum creatinine (mg/dL) Females: Creatinine CL (mL/min) = [Weight (kg) x (140 – Age) / 72 x serum creatinine (mg/dL)] x 0.85 13. Female subjects had been non-reproductive potential (ie, post-menopausal by history: ≥ 60 years old and no menses for ≥ 1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR

	history of bilateral oophorectomy) or had a negative serum pregnancy test upon study entry. 14. Subject was willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up. <u>Key Exclusion criteria:</u> Subjects who met any of the following criteria were excluded from this study: 1. Involvement in the planning and/or conduct of the study. 2. Participation in another clinical study with an investigational product during the last 4 weeks. 3. WHO Classification G3 neuroendocrine neoplasms of lung origin (oat cell/large cell lung cancer). 4. Prior treatment with anti-PDL-1/anti-PD-1 or anti-CTL-4 therapy. 5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diathesis including any subject known to have evidence of acute or chronic hepatitis B (e.g., HBsAg reactive), hepatitis C (e.g., HCV RNA [qualitative] was detected) or known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or psychiatric illness/social situation that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent. 6. Known history of previous clinical diagnosis of tuberculosis. 7. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab or tremelimumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which were not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

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	8. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) were not excluded. 9. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis). 10. History of allogeneic organ transplant. 11. History of hypersensitivity to durvalumab, tremelimumab or any excipient. 12. Subjects who had a diagnosis of immunodeficiency or were receiving systemic steroid therapy or any other form of immunosuppressive therapy within 28 days prior to the first dose of trial treatment. 13. Knowledge of active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they have stable brain metastases [without evidence of progression by imaging confirmed [by magnetic resonance imaging (MRI) if MRI was used at prior imaging, or confirmed by computed tomography (CT) imaging if CT used at prior imaging] for at least four week prior to the first dose of trial treatment; also, any neurologic symptoms had returned to baseline], had no evidence of new or enlarging brain metastases,and had not used steroids for brain metastases for at least 7 days prior to trial treatment. This exception did not include carcinomatous meningitis, as subjects with carcinomatous meningitis were excluded regardless of clinical stability. 14. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab or tremelimumab. Note: The killed virus vaccines used for seasonal influenza vaccines for injection were allowed; however intranasal influenza vaccines (e.g., FluMist®) were live attenuated vaccines, and were not allowed. 15. Subjects having a known history of, or any evidence of interstitial lung disease or active, noninfectious pneumonitis. 16. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1.

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	17. Subjects who had received any anti-cancer treatment within 21 days or any investigational agent within 30 days prior to the first dose of study drug and had recovered from any toxicity related to previous anti-cancer treatment. This did not apply to the use of somatostatin analogues for symptomatic therapy. 18. Major surgery within 3 weeks prior to the first dose of study drug. 19. Subjects having > 1+ proteinuria on urine dipstick testing were to undergo 24h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥ 1 g/24h were ineligible. 20. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina; myocardial infarction or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment. 21. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction. 22. Bleeding or thrombotic disorders or use of anticoagulants, such as warfarin, or similar agents requiring therapeutic international normalized ratio (INR) monitoring. Treatment with low molecular weight heparin (LMWH) was allowed. 23. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug. 24. Patients with tumoral disease in the head and neck region, such as paratracheal or periesophageal lymph node involvement, or with infiltration of structures in the digestive tract, or vascular pathways that represent a risk of increased bleeding. 25. Patients of cohort 1 with neuroendocrine tumors of pulmonary origin or pulmonary metastases with evidence of active bleeding. 26. Patients with evidence of digestive bleeding. 27. Active infection (any infection requiring treatment).

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	28. Active malignancy (except for differentiated thyroid carcinoma, or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 24 months. 29. Female patients who were pregnant or breastfeeding or male or female patients of reproductive potential who were not willing to employ highly effective birth control from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever was the longer time period. 30. Documented active alcohol or drug abuse. 31. Patients with a prior history of non-compliance with medical regimens. 32. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
Test product, dose and mode of administration	<u>Products:</u> 1- Durvalumab (IMFINZI) ATC code: Antineoplastic agents, monoclonal antibodies L01FF03 2-Tremelimumab ATC code: None <u>Dose:</u> Patients received 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 1500 mg durvalumab monotherapy q4w starting on Week 16 for up to 8 months (9 doses). Dosing outside the window should had been discussed with the Study Physician. Tremelimumab was administered first. Durvalumab infusion was started approximately 1 hour after the end of tremelimumab infusion. The duration was approximately 1 hour for each infusion. A 1-hour observation period was required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions were observed

	during or after the first cycle, subsequent infusion observation periods could be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion). <u>Mode of administration:</u> Durvalumab: Solution for intravenous (IV) infusion Tremelimumab: Solution for intravenous (IV) infusion
Duration of treatment	Retreatment was allowed (once only) for patients meeting the retreatment criteria below. The same treatment guidelines followed during the initial 12-month treatment period were followed during the retreatment period, including the same dose and frequency of treatments and the same schedule of assessments. Patients who received the combination of durvalumab and tremelimumab were retreated in 2 clinical scenarios, described below: 1. Patients who achieved and maintained disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period may restart treatment with the combination upon evidence of PD, with or without confirmation according to RECIST 1.1, during follow-up. 2. Patients who completed the 4 dosing cycles of the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently was evidenced of PD during the durvalumab monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, restarted the treatment with the combination. Before restarting their assigned treatment, the Investigator had been ensured that the patient: 1. Did not have any significant, unacceptable, or irreversible toxicities that indicated continuing treatment was not beneficial to the patient. 2. Still fulfilled the eligibility criteria for this study, including re-consenting to restart durvalumab and tremelimumab. 3. Did not receive an intervening systemic anticancer therapy after their assigned treatment discontinuation.

	4. A baseline tumor assessment was performed within 28 days of restarting their assigned treatment; all further scans were performed at the same frequency as during the initial 12 months of treatment (relative to the date of randomization) until study treatment was stopped (maximum of 12 months of further treatment). During the retreatment period, patients that received durvalumab + tremelimumab could resume durvalumab dosing at 1500 mg q4w with 75 mg of tremelimumab q4w for 4 doses each. Patients then continued durvalumab monotherapy at 1500 mg q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy (a total of 9 additional doses). Treatment through progression was at the Investigator's discretion, and the Investigator had been ensured that patients did not have any significant, unacceptable, or irreversible toxicities that indicated that continuing treatment did not further benefit the patient. A patient with a confirmed progression receiving durvalumab + tremelimumab could not continue therapy or obtain retreatment if dosing was ongoing in the combination portion of therapy (q4w dosing) and progression occurred in a target lesion that had previously shown a confirmed response. Patients who were determined by the sponsor and/or the Investigator to be unable to continue treatment entered follow-up.
Criteria for evaluation	<u>Primary Objective</u> -Primary endpoint for cohorts 1, 2 and 3: Nine-months clinical benefit rate (CBR) by Response Evaluation Criteria In Solid Tumors (RECIST 1.1), which was defined as the percentage of patients achieving complete response (CR), partial response (PR), or stable disease (SD) at month 9 after durvalumab plus tremelimumab was started. -Primary endpoint for cohort 4: Nine-months overall survival rate, which was defined as the percentage of patients alive at month 9 after durvalumab plus tremelimumab was started.

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	Secondary Objective -Overall response rate (ORR) by irRECIST. -To assess the duration of response according to irRECIST. -To assess the median progression-free survival time (PFS) according to irRECIST. -To assess the safety profile of Durvalumab and Tremelimumab in subjects with advanced neuroendocrine neoplasms. -To assess the median overall survival (OS) time. -To assess response status according to irRECIST at 6, 9 and 12 months after the start of study treatment. Exploratory Objective(s) -To evaluate biochemical response (changes in CgA and NSE levels) and its association with response rate and progression-free survival. -To assess whether baseline tumor and blood biomarkers may be predictive of response to durvalumab and tremelimumab therapy. -To explore additional hypotheses related to biomarkers and relationship to durvalumab and tremelimumab efficacy and/or toxicity and neuroendocrine tumors evolution that may arise from internal or external research activities. Study procedures Screening procedures were performed up to 28 days before Day 1, unless otherwise specified. All subjects first read, understand, and sign the IEC-approved ICF before any study-specific screening procedures were performed. After signing the informed consent form (ICF), completing all screening procedures, and being deemed eligible for entry, subjects were

enrolled in the study. Procedures performed prior to the signing of the ICF were considered standard of care and used as screening assessments if they fell within the 28-day screening window.

The following procedures were performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vital signs, weight and height
- 12-lead ECG (in triplicate [2-5 minutes apart])
- Review of prior/concomitant medications
- Record any AEs or SAEs (since ICF signature)
- Imaging by CT/MRI
- Review of octreoscan/PET (up to 6 months prior inclusion) only on cohorts 1 to 3.
- Collect blood samples for biomarkers analysis
- Archival tumor block or slides
- Clinical laboratory tests for:
    - Hematology
    - Clinical chemistry
    - TSH, fT3 and fT4
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum pregnancy test (for women of childbearing potential only)
    - Hepatitis and HIV serologies
    - Urinalysis
    - Disease-specific tumor markers

<u>Treatment Phase</u>

Procedures to be conducted during the treatment phase of the study were presented in the Schedule of Assessments. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) did not need to be repeated on C1D1.

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	Efforts had been made to conduct study visits on the day scheduled (± 1 day). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Visits and Procedures. Results of the laboratory assessments had been reviewed always prior to each cycle dose administration. Whenever possible, subjects had been evaluated at approximately the same time of the day (e.g., morning or afternoon) at each visit, and reasonable efforts had been made to conduct all evaluations in the same test order at each visit. Tumor assessments had been performed at time points indicated in the Schedule of Visits and Procedures. **Cycle 1/Day 1** ● Obtain vital signs (resting BP, HR, RR, body temperature) and weight. ● Physical examination was not mandatory if performed at baseline (day -1) ; however a symptom-directed physical examination was performed on Cycle 1/Day 1 and at any time during the study, as clinically indicated. ● Administer study drug: ◦ Record all concomitant medication use. ◦ Record any AEs or SAEs. **Cycle 1/Day 15** ● Obtain vital signs (resting BP, HR, RR, body temperature) and weight. ● Evaluate ECOG performance status. ● Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination was performed at any time during the study, as clinically indicated. ● Collect blood samples for biochemistry and hematology analyses, including TSH, fT3 and fT4. ● Urinalysis ● Record all concomitant medication use. ● Record any AEs or SAEs. **Cycle 2/Day 1**

	● Evaluate ECOG performance status. ● Obtain vital signs (supine BP, HR, RR, body temperature) and weight. ● Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination was performed at any time during the study, as clinically indicated. ● Collect blood samples for biochemistry and hematology analyses including TSH, fT3 and fT4. ● Urinalysis. ● Administer study drug. ● Collect blood samples for biomarker analysis. ● Record all concomitant medication use. ● Record any AEs or SAEs. ● Record survival data. **Cycle 2/Day 15** ● Evaluate ECOG performance status. ● Obtain vital signs (supine BP, HR, RR, body temperature) and weight. ● Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination was performed at any time during the study, as clinically indicated. ● Collect blood samples for biochemistry and hematology analyses including TSH, fT3 and fT4. ● Urinalysis. ● Record all concomitant medication use. ● Record any AEs or SAEs. **Cycle 3/Day 1** ● Evaluate ECOG performance status. ● Obtain vital signs (supine BP, HR, RR, body temperature) and weight. ● Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination was performed at any time during the study, as clinically indicated. ● Collect blood samples for biochemistry and hematology analyses, including TSH, fT3 and fT4.

	● Urinalysis. ● Administer study drugs. ● Record all concomitant medication use. ● Record any AEs or SAEs. ● Record Survival data. **Cycle 3/Day 15** ● Evaluate ECOG performance status. ● Obtain vital signs (supine BP, HR, RR, body temperature) and weight. ● Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination was performed at any time during the study, as clinically indicated. ● Collect blood samples for biochemistry and hematology analyses, including TSH, fT3 and fT4. ● Urinalysis. ● Record all concomitant medication use. ● Record any AEs or SAEs. **Cycle 4 Through Last Cycle (cycle 12)/Day 1** ● Evaluate ECOG performance status. ● Obtain vital signs (supine BP, HR, RR, body temperature) and weight. ● Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination was performed at any time during the study, as clinically indicated. ● Collect blood samples for biochemistry and hematology analyses, including TSH, fT3 and fT4 ● Urinalysis. ● Administer study drugs. (from C5D1 to C12D1 tremelimumab was no longer administered, only durvalumab). ● Record all concomitant medication use. ● Record any AEs or SAEs. ● Record survival data. ● Tumor assessment every 12 weeks until confirmed PD. **End of Treatment**

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	End of treatment was defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinued durvalumab or tremelimumab prior to 12 months, end of treatment was considered the last visit where the decision was made to discontinue treatment. All required procedures were completed within ± 7 days of the end of treatment visit. Repeat disease assessment was not required if performed within 28 days prior to the end of treatment visit. Blood samples for biomarker analysis were collected. All subjects were followed for survival until the end of the study regardless of further treatments, or until the sponsor ended the study. **Follow-up period** TC/MRI every 12 weeks until progression. Monthly visits during the first 3 months after the end of treatment, every 2 months until one year, and therefore every 6 months.
Statistical methods	Patients were consecutively included, in compliance with the previously established inclusion criteria. The required number of patients was calculated using a one-sample Superiority test (function One Sample Proportion. NIS of the Trial Size package of R software). According to previous knowledge, it was estimated that the reference value for the likelihood to be progression-free at 9 months was 30% and we expected an increase of 20% with a superiority margin of 10%. With a unilateral alpha level of 5% and 80% power, we estimated to include 28 patients per group, with an expected lost to follow-up rate of 10%, a final sample size in each 1, 2 and 3 cohort were 31 patients included. For cohort 4, and according to previous knowledge, it was estimated that the reference proportion of patients being alive at 9 months was 13% and we expected an increase of 10% with a superiority margin of 5%. With a unilateral alpha level of 5% and 80% power, we estimated to include 30 patients per group, with an expected lost to follow-up rate of 10%, a final sample size was 33 patients included. Summarizing, the total sample size was 126 patients: 31 patients for cohorts 1 to 3, and 33 patients for cohort 4. Efficacy analysis was based on the full analysis set that included all enrolled patients. Safety was assessed on the safety analysis set that included all patients

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	who received at least one dose of durvalumab or tremelimumab. Continuous variables were summarized using descriptive statistics (n, mean, standard deviation, range, and median). Frequency counts and the percentage of subjects within each category were provided for categorical data. Response rates were estimated using 95% confidence intervals (CI) or full range intervals. Multivariate regression models were used to analyze the potential relationship between exploratory variables and primary endpoints. The survival or time-to-event endpoints were estimated using the Kaplan–Meier method and Cox regression analysis to obtain hazard ratios and CIs. Patients without documented progression or death at the time of the analysis were censored at the last date of tumor evaluation for PFS assessment. Patients without documented death at the time of the analysis were censored at the last date of follow-up for OS assessment. All statistical tests were considered two-tailed, and results with $p < 0.05$ were considered significant. All statistical analyses were performed with R and SPSS (IBM SPSS Statistics Version 26, Armonk, NY).
Results	- **Baseline patient characteristics** Between April 2017 and December 2019, 123 patients were enrolled in the study (Fig.1). Concisely, there were 27 typical or atypical lung carcinoids (Cohort 1); 31 G1-2 gastrointestinal (Cohort 2); 32 G1-2 pancreatic (Cohort 3); and 33 high grade (grade 3) GEP (Cohort 4) NENs. All patients received at least one dose of durvalumab plus tremelimumab (Fig.1 and Table 1). - **Efficacy endpoints** Overall DCR according to RECIST 1.1 was 56.1% (95% CI: 47.3-64.6), and 66.7% (95% CI: 47.9-82.1), 74.2% (95% CI: 57.1-87.0), 59.4% (95% CI: 42.2-75.0), and 27.3% (95% CI: 14.4-43.9) for all included patients, and Cohorts 1 to 4 respectively (Table 2). The 9-m DCR was 22.8% (95% CI: 16.0-30.8) for the full dataset, and 25.9% (95% CI: 12.4-44.3), 35.5% (95% CI: 20.5-53.0), 25% (95% CI: 12.6-41.7), and 6.1% (95% CI: 1.3-18.1) for Cohorts 1 to 4 respectively (Table 2). In the full analysis set, ORR was 6.5% (95% CI: 3.1-11.9); 1 (0.8%) patient had CR, 7 (5.7%) PR, and 61 (49.6%) SD as their best response throughout the study according to RECIST. 1.1 (Table 2 and Fig.2). No statistically significant differences were found between evaluation according to RECIST 1.1 or irRECIST 1.1 in the full analysis set or within any cohort (Table 2). The median DoR was 10.4 months (range: 2.7-24.3), whereas SD was maintained during a median time

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	of 5.5 months (range: 0.9-30.7)(Fig.3). There was no statistically significant correlation between response and PD-L1 expression by CPS (Table 3). With a median follow up of 16.5 months (range: 0.3-42.9), the median PFS for the full analysis set according to irRECIST 1.1 was 5.3 months (95% CI: 4.4-6.2). In the Cohorts 1 to 4, specifically, the median PFS was 5.6 (95% CI: 4.9-6.2), 5.8 (95% CI: 3.1-8.5), 5.5 (95% CI: 2.4-8.7), and 2.4 (95% CI: 2.1-2.8) months, respectively (Fig.4A). No statistically significant differences were found in PFS based on PD-L1 CPS (Fig.4B-E). A total of 77 (62.6%) patients died throughout the study period, due to disease progression 69 (56.1%), toxicity 3 (2.4%), clinical deterioration 1 (0.8%), carcinoid crisis 1 (0.8%), progression of secondary neoplasm 1 (0.8%), cerebrovascular incident 1 (0.8%), and Non-COVID-19 pneumonia 1 (0.8%). The median OS for the full dataset was 22.6 months (95% CI: 16.6-28.6). The median OS was not reached in lung NECs (Cohort 1) and was 29.5 (95% CI: 19.6-39.4), 23.8 (95% CI: 16.4-31.2), and 5.9 (95% CI: 2-9.7) months for cohorts 2 to 4, respectively (Fig.5). For high-grade GEP-NENs (Cohort 4), the 9-m OS rate, which was the primary endpoint, was 36.1% (95% CI: 19.6-52.6), surpassing the pre-established futility threshold. Moreover, 10 (30.3%) patients with GEP-NENs surpassed the 12 months survival (long-survivors). A stratified analysis for OS within grade 3 GEP-NENs did not find statistically significant associations between survival status and baseline characteristics, or PD-L1 CPS status (Table 4). - **Safety** Overall, only 16 (13%) patients completed the treatment as initially scheduled and most patients discontinued prematurely (87%) mainly due to: PD 74 (60.2%), unacceptable toxicity 12 (9.8%), death 6 (4.9%) or physician criteria 4 (3.3%) (Fig.1). The median number of administered cycles was 5 for durvalumab and 4 for tremelimumab. Most treatment-related adverse events (TRAEs) were mild and resolved with appropriate clinical care; being the most common across cohorts: fatigue (44.7%), diarrhea (32.5%) and pruritus (23.6%) (Table 5). Grade ≥ 3 toxicities had low frequency, and most common were diarrhea (6.5%), transaminitis (4.9%), fatigue (3.3%), and vomiting (2.4%) (Table 5). Deaths due to toxicity were hepatic failure, myasthenia gravis, and diarrhea with encephalitis infection.

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Discussion	Treatment with durvalumab plus tremelimumab showed modest activity in this large cohort (n = 123) of heavily pretreated NEN patients, regardless of their origin, histological grade, differentiation or PD-L1 expression. Long-term disease control rate was chosen as the primary endpoint to include long-term stabilization of the disease as a therapeutic success. The overall DCR of 56.1% (RECIST 1.1) did not improve those reported with single ICI with pembrolizumab (59.8%) or spartalizumab (63.2%) [1,2]. Responses to treatment were scarce, documented only in 8 (6.5%) patients, and similar to single ICI, or dual ICI with an ORR of 14.9% in advanced lung or GEP NENs [1-4]. Patients with lung-NENs were previously identified as a potentially interesting group for immunotherapy, with ORR that ranged from 18.2% to 20% [2,4]. Conversely, lung-NETs in our study had an ORR of 11.1%, which pointed out a limited activity for durvalumab plus tremelimumab in this setting. Our results also showed no enrichment of activity regarding histological grade, with modest activity also in high-grade NENs (ORR 9.1%). This differs from early experience with nivolumab plus ipilimumab, which showed an ORR up to 44% in patients with high-grade NENs previously treated with chemotherapy [5]. Due to the indirect nature of the comparison our findings should be interpreted with caution when compared to those of previous trials, which might involve low or high risk patients. For instance, the DART trial excluded pancreatic NENs [5]. DoR achieved by immunotherapy in our trial and previous reports in low-grade NENs still remain distant to those recently described with targeted therapies such as lenvatinib, with a median of 21.5 months (range: 8.4-38.3) [6]. The median overall PFS was 5.3 months, which is in range with that reported with single-agent pembrolizumab after progression to standard therapies, median 4.1 months (95% CI: 3.5-5.4) [1]; or nivolumab plus ipilimumab, median 4 months (95% CI: 3-6) [5]. Two previous trials in patients with low-grade NENs with single-agent pembrolizumab reported a median OS that ranged from 21 to 24 months, which was in range of the OS among patients with low-grade NENs in our study, suggest a small benefit of adding CTLA4 blockade [1,3]. Previous trials using dual ICI also failed to improve survival [4,5]. In high-grade NENs, durvalumab plus tremelimumab showed a modest improvement in survival, surpassing the pre-established futility threshold. Ten patients achieved prolonged survival, longer than 12 months, suggesting the potential use of dual ICI in a selected subtype of patients within this

setting. Long survivors had mostly poorly differentiated NECs (70%), however no molecular or clinical biomarker at baseline had a significant correlation with treatment efficacy in this subgroup.

The differences observed in the efficacy and activity of immunotherapy between low- and high-grade NENs across trials may rely on the higher PD-L1 expression, TMB and enhanced neoantigen presentation which has been positively correlated to tumor grade [7]. Tumor PD-L1 expression has been associated with ICI efficacy across tumor types and positively associated with poorer survival in NENs [8]. However, we did not observe correlation of PD-L1 CPS with efficacy. Another possible rationale would be the potential immunogenic effect attributable to chemotherapy, which is the standard first-line treatment for high grade GEP-NENs. Platinum-based chemotherapy is capable of modulating tumor-infiltrating lymphocytes (TILs) and reactivating antitumor immunity within an immuno-suppressive microenvironment [9,10]. In fact, two phase III trials demonstrated benefit in survival with the addition of durvalumab or atezolizumab to first-line platinum-etoposide [11,12]. Based on these findings, the administration of dual ICI in combination with standard first-line chemotherapy may be considered a reasonable option to explore in high-grade NENs.

Regarding safety, our findings are consistent with previous reports [11]. Premature treatment discontinuation was required in most patients (87%), which likely impacted efficacy.

The main limitation of the DUNE trial was the lack of randomization and a parallel control group comparing single ICI or alternative treatment options. There is limited information on prognosis and survival in such a heavily pre-treated population of NENs, which may have led to an overestimation of the expected primary endpoints. Despite overall sample size being relevant, the sample size for each cohort limited the exploratory research of potential prognostic factors in the stratified analysis. The small sample size also limited the comparison between G3 NET vs NEC histology, which are tumors with very different behaviour. However, a centralized review by an experienced pathologist showed that long-term survivors included both NECs and NETs. The lack of a centralized review for the tumour assessment was another caveat. In contrast, histological differentiation and PD-L1 CPS were centrally reviewed, and differences in ORR attributable to the use of RECIST 1.1 or irRECIST criteria were excluded.

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	In summary, our findings support a potential modest use of dual ICB in high-grade NENs. Further research with ICB in this setting may focus on long-term survival endpoints, and potentially shifting to a first-line setting in combination with chemotherapy. Prognostic and predictive biomarkers need to be further characterized in patients treated with ICB.

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Figures and Tables

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Table 1. Baseline patient characteristics

Characteristic	Lung-NENs (N = 27)	G1/2 GI-NETs (N = 31)	G1/2 pan-NETs (N = 32)	G3 GEP-NENs (N = 33)	DUNE trial (N = 123)
Median age (range); years	62 (34-83)	63 (38-84)	66 (47-86)	55 (34-78)	62 (34-86)
Gender; n (%)					
Male	18 (66.7)	18 (58.1)	14 (43.8)	22 (66.7)	72 (58.5)
Female	9 (33.3)	13 (41.9)	18 (56.3)	11 (33.3)	51 (41.5)
ECOG PS; n (%)					
score 0	11 (40.7)	13 (41.9)	16 (50)	13 (39.4)	53 (43.1)
score 1	16 (59.3)	18 (58.1)	16 (50)	20 (60.6)	70 (56.9)
Histopathological diagnosis (central review); n (%) [a]					
well differentiated / Typical / NET [a]	21 (77.8)	28 (90.3)	29 (90.6)	15 (45.5)	93 (75.6)
moderately differentiated / Atypical /NET [a]	6 (22.2)	3 (9.7)	3 (9.4)	0 (0)	12 (9.8)
poorly differentiated /NEC [a]	0 (0)	0 (0)	0 (0)	18 (54.5)	18 (14.6)
Clinical stage, n (%)					
I - III	8 (29.6)	1 (3.2)	1 (3.1)	3 (9.1)	13 (10.6)
IV	18 (66.7)	30 (96.8)	31 (96.9)	30 (90.9)	109 (88.6)
Uk	1 (3.7)	0 (0)	0 (0)	0 (0)	1 (0.8)
Ki-67; n (%)					

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< 2	1 (3.7)	6 (19.4)	1 (3.1)	0 (0)	8 (6.5)
2-20	19 (70.4)	25 (80.6)	31 (96.9)	0 (0)	75 (61)
> 20	5 (18.5)	0 (0)	0 (0)	33 (100)*	38 (30.9)
Uk	2 (7.4)	0 (0)	0 (0)	0 (0)	2 (1.6)
PD-L1 Combined Positive Score (central review); n (%)					
Negative (0 - 1)	13 (48.1)	22 (71)	16 (50)	14 (42.4)	65 (52.8)
Positive (> 1)	6 (22.2)	3 (9.7)	5 (15.6)	7 (21.2)	21 (17.1)
Uk	8 (29.6)	6 (19.4)	11 (34.4)	12 (36.4)	37 (30.1)
Previous lines; n (%)					
1	15 (55.6)	12 (38.7)	1 (3.1)	33 (100)	61 (49.6)
2	10 (37)	12 (38.7)	14 (43.8)	0 (0)	36 (29.3)
≥ 3	2 (7.4)	7 (22.6)	17 (53.1)	0 (0)	26 (21.1)
Type of previous lines, n (%)					
Chemotherapy (CT)	5 (18.5)	7 (22.6)	16 (50)	0 (0)	28 (22.8)
Platinum-based CT	0 (0)	0 (0)	0 (0)	33 (100)	33 (26.8)
SSA	22 (81.5)	29 (93.5)	25 (78.1)	2 (6.1)	78 (63.4)
Everolimus	17 (63)	19 (61.3)	25 (78.1)	0 (0)	61 (49.6)
Sunitinib	0 (0)	2 (10.5)	18 (56.3)	0 (0)	20 (16.3)
Radiopharmaceuticals	0 (0)	6 (19.4)	3 (9.4)	0 (0)	9 (7.3)
Others	11 (40.1)	17 (54.8)	20 (62.5)	5 (15.6)	53 (43.1)

* In high grade GEP-NENs 20 (60.6%) patients had Ki-67 > 50.

[a] Well / poorly differentiated categories apply to cohorts 1-3 (low grade NENs). Typical / atypical categories apply to cohort 1 (Lung NENs). NET / NEC categories apply to cohort 4 (G3 GEP NENs).

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SSA, Somatostatin analogues; CT, Chemotherapy; PD-L1, Programmed Death ligand 1; GEP, Gastroenteropancreatic; GI, gastrointestinal; NECs, neuroendocrine carcinomas; NENs, neuroendocrine neoplasms; NETs, neuroendocrine tumors; pan, pancreatic.

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Table 2. Durvalumab plus Tremelimumab efficacy

		Lung-NENs (N = 27)*	**G1/2 GI-NETs (N = 31)***	**G1/2 pan-NETs (N = 32)***	**G3 GEP-NENs (N = 33)***	**DUNE trial (N = 123)**
RECIST 1.1	Best Overall response, n (%)					
	CR	0 (0)	0 (0)	0 (0)	1 (3)	1 (0.8)
	PR	3 (11.1)	0 (0)	2 (6.3)	2 (6.1)	7 (5.7)
	SD	15 (55.6)	23 (74.2)	17 (53.1)	6 (18.2)	61 (49.6)
	PD	7 (25.9)	6 (19.4)	10 (31.3)	20 (60.6)	43 (35)
	ORR; % (95% CI)	11.1 (3.2-26.8)	0 (0)	6.3 (1.3-18.6)	9.1 (2.6-22.3)	6.5 (3.1-11.9)
	DCR; % (95% CI)	66.7 (47.9-82.1)	74.2 (57.1-87.0)	59.4 (42.2-75.0)	27.3 (14.4-43.9)	56.1 (47.3-64.6)
	DCR 9m Rate; % (95% CI)	25.9 (12.4-44.3)	35.5 (20.5-53.0)	25 (12.6-41.7)	6.1 (1.3-18.1)	22.8 (16.0-30.8)
ir RECIST 1.1	Best Overall response, n (%)					
	CR	0 (0)	0 (0)	0 (0)	1 (3)	1 (0.8)
	PR	3 (11.1)	0 (0)	2 (6.3)	2 (6.1)	7 (5.7)
	SD	18 (66.7)	23 (74.2)	18 (56.3)	7 (21.2)	66 (53.7)
	PD	6 (22.2)	8 (25.8)	12 (37.5)	23 (69.7)	49 (39.8)
	ORR; % (95% CI)	11.1 (3.2-26.8)	0 (0)	6.3 (1.3-18.6)	9.1 (2.6-22.3)	6.5 (3.1-11.9)
	DCR; % (95% CI)	77.8 (59.8-90.2)	74.2 (57.1-87.0)	62.5 (45.2-77.6)	30.3 (16.8-47.1)	60.2 (51.4-68.5)
	DCR 9m Rate; % (95% CI)	25.9 (12.4-44.3)	35.5 (20.5-53.0)	25 (12.6-41.7)	6.1 (1.3-18.1)	22.8 (16.0-30.8)
DoR; median (range); m		3 (2.7 -15.5)	-	16.3 (10.6-22)	10.1 (3.9-24.3)	10.4 (2.7-24.3)
p Value **(RECIST 1.1 vs irRECIST 1.1)[1]**		<0.001	<0.001	<0.001	<0.001	<0.001

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1 Cohen's kappa test compares the distribution of best objective responses within each cohort and in the full dataset. The test measures the agreement between both methods, if p-value is significant (<0.05) means that the agreement is significant and both methods are equivalent at statistical level.
* Two patients in C1 and C2, three patients in C3, and four patients in C4 were only evaluated by irRECIST and not evaluated by RECIST.

Abbreviations: ORR, Objective Response Rate; DCR, Disease Control Rate; DoR, Duration of the Response; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progression disease; RECIST, Response evaluation criteria in solid tumors; GEP, Gastroenteropancreatic; GI, gastrointestinal; NECs, neuroendocrine carcinomas; NENs, neuroendocrine neoplasms; NETs, neuroendocrine tumors; pan, pancreatic.

Table 3. ORR vs PD-L1

		Lung-NENs (N = 27)		**G1/2 GI-NETs (N = 31)**		**G1/2 pan-NETs (N = 32)**		**G3 GEP-NENs (N = 33)**	
PD-L1 CPS		Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
ORR n (%)	**Yes**	0 (0)	2 (33.3)	0 (0)	0 (0)	0 (0)	1 (20)	1 (7.1)	0 (0)
	No	13 (100)	4 (66.7)	22 (100)	3 (100)	16 (100)	4 (80)	13 (92.9)	7 (100)
p-value [1]		0.088		-		0.238		1.000	

ORR: calculated as the best response during treatment by irRECIST 1.1; PD-L1 CPS assessed by centralized review. 1: Fisher Exact test.

Table 4. OS vs PD-L1

Characteristic	**No long-survivors (OS <12m) (N = 23)**	**Long-survivors (OS >12m) (N = 10)**	***p-value***
Median age (range); years	55 (34-78)	57 (42-75)	0.875 [1]
Gender; n (%)			
Male	14 (60.9)	8 (80)	0.430 [2]
Female	9 (39.1)	2 (20)	
ECOG PS; n (%)			
score 0	7 (30.4)	6 (60)	0.139 [2]
score 1	16 (69.6)	4 (40)	
Histopathological diagnosis (central review); n (%)			
NET	12 (52.2)	3 (30)	0.283 [2]

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NEC	11 (47.8)	7 (70)	
Clinical stage, n (%)			
III	1 (4.3)	2 (20)	0.073 [2]
IV	22 (95.7)	8 (80)	
Ki-67; n (%)			
> 20	9 (39.1)	4 (40)	1.000 [2]
> 50	14 (60.9)	6 (60)	
Extranodal locations; n (%)			
0-2	3 (13)	4 (40)	0.276 [2]
> 2	5 (21.7)	1 (10)	
Uk	15 (65.2)	5 (50)	
PD-L1 Combined Positive Score (central review); n (%)			
Negative (0 - 1)	10 (43.5)	4 (40)	0.624 [2]
Positive (> 1)	6 (26.1)	1 (10)	
Uk	7 (30.3)	5 (50)	

1: U of Mann Whitney test; 2: Fisher Exact test.
Abbreviations: NECs, neuroendocrine carcinomas; NETs, neuroendocrine tumors; OS, overall survival; PD-L1, programmed death ligand 1; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 5. Durvalumab plus Tremelimumab safety. Most prevalent Treatment-related Adverse Events according to maximum grade (Common Terminology Criteria for Adverse Events, v.4.03). Only TRAEs with frequency ≥ 5 %.

Event; n (%)	**Lung-NENs (N = 27)**		**G1/2 GI-NETs (N = 31)**		**G1/2 pan-NETs (N = 32)**		**G3 GEP-NENs (N = 33)**		**DUNE trial (N = 123)**	
	Any grade	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Fatigue	8 (29.6)	2 (7.4)	15 (48.4)	0 (0)	20 (62.5)	2 (6.3)	12 (36.4)	0 (0)	55 (44.7)	4 (3.3)

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Diarrhea	11 (40.7)	1* (3.7)	12 (38.7)	3 (9.7)	11 (34.4)	2 (6.3)	6 (18.2)	2 (6.1)	40 (32.5)	8 (6.5)
Pruritus	4 (14.8)	0 (0)	10 (32.3)	0 (0)	10 (31.3)	0 (0)	5 (15.2)	0 (0)	29 (23.6)	0 (0)
Náusea	1 (3.7)	0 (0)	6 (19.4)	0 (0)	8 (25)	0 (0)	3 (9.1)	1 (3)	18 (14.6)	1 (0.8)
Hypothyroidism	2 (7.4)	1 (3.7)	5 (16.1)	0 (0)	2 (6.3)	0 (0)	4 (12.1)	0 (0)	13 (10.6)	1 (0.8)
Arthralgia	2 (7.4)	0 (0)	4 (12.9)	0 (0)	6 (18.8)	0 (0)	1 (3)	0 (0)	13 (10.6)	0 (0)
Vomiting	2 (7.4)	1 (3.7)	3 (9.7)	0 (0)	3 (9.4)	1 (3.1)	4 (12.1)	1 (3)	12 (9.8)	3 (2.4)
Skin and subcutaneous disorders	3 (11.1)	0 (0)	3 (9.7)	0 (0)	5 (15.6)	0 (0)	1 (3)	0 (0)	12 (9.8)	0 (0)
Mucositis oral	2 (7.4)	0 (0)	2 (6.5)	0 (0)	5 (15.6)	0 (0)	2 (6.1)	0 (0)	11 (8.9)	0 (0)
Gastrointestinal disorders	4 (14.8)	0 (0)	6 (19.4)	0 (0)	1 (3.1)	0 (0)	0 (0)	0 (0)	11 (8.9)	0 (0)
Anorexia	2 (7.4)	0 (0)	4 (12.9)	0 (0)	1 (3.1)	0 (0)	4 (12.1)	0 (0)	11 (8.9)	0 (0)
Rash	0 (0)	0 (0)	5 (16.1)	0 (0)	4 (12.5)	0 (0)	1 (3)	0 (0)	10 (8.1)	0 (0)
Abdominal pain	2 (7.4)	0 (0)	5 (16.1)	0 (0)	2 (6.3)	0 (0)	1 (3)	0 (0)	10 (8.1)	0 (0)
Constipation	1 (3.7)	0 (0)	1 (3.2)	0 (0)	6 (18.8)	0 (0)	1 (3)	0 (0)	9 (7.3)	0 (0)
Rash maculo-papular	1 (3.7)	0 (0)	1 (3.2)	0 (0)	2 (6.3)	0 (0)	4 (12.1)	0 (0)	8 (6.5)	0 (0)
AST increased	0 (0)	0 (0)	1 (3.2)	1 (3.2)	6 (18.8)	5 (15.6)	1 (3)	0 (0)	8 (6.5)	6 (4.9)
ALT increased	0 (0)	0 (0)	1 (3.2)	1 (3.2)	7 (21.9)	5 (15.6)	0 (0)	0 (0)	8 (6.5)	6 (4.9)

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Dry skin	0 (0)	0 (0)	4 (12.9)	0 (0)	2 (6.3)	0 (0)	1 (3)	0 (0)	7 (5.7)	0 (0)

*One patient died as a consequence of treatment-related diarrhea and encephalitis infection G5.
One patient died as a consequence of treatment-related hepatic failure G5.
One patient died as a consequence of treatment-related myasthenia gravis G5.
One patient died as a consequence of treatment-related upper respiratory infection G5.
Abbreviations: TRAE, Treatment-related Adverse Event; GEP, Gastroenteropancreatic; GI, gastrointestinal; NECs, neuroendocrine carcinomas; NENs, neuroendocrine neoplasms; NETs, neuroendocrine tumors; pan, pancreatic.

FIGURES

Figure 1. Patient distribution and treatment compliance

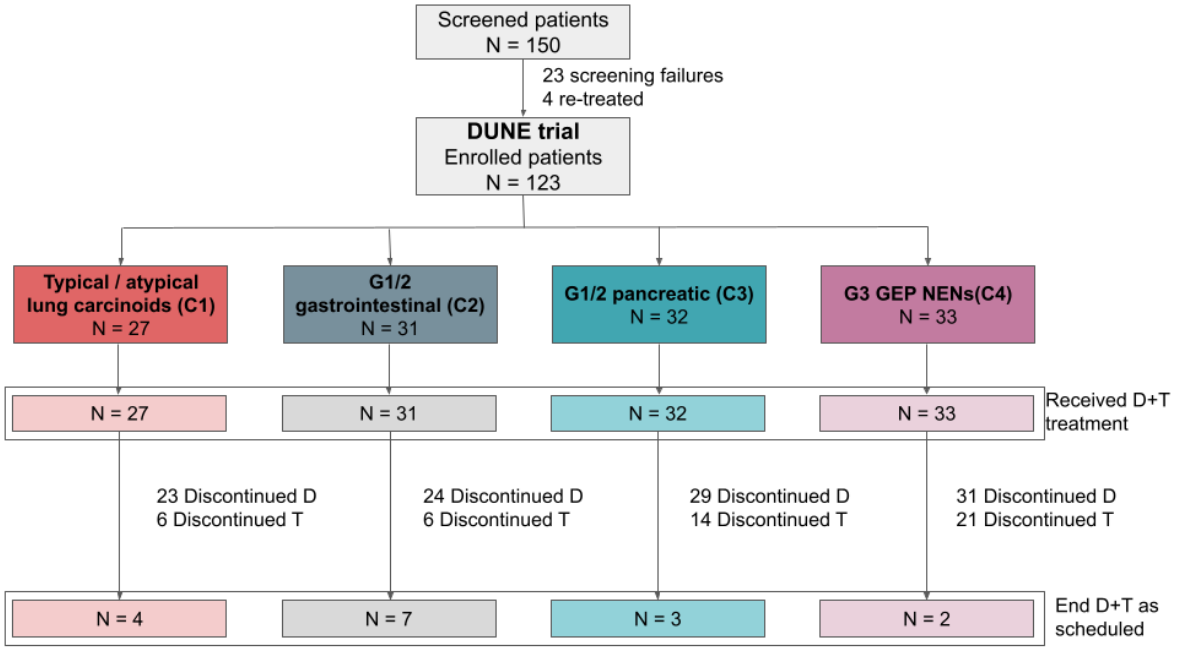

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Figure 2. ORR for each cohort; A) Typical / atypical lung carcinoids; B) low grade (Grade 1-2) gastrointestinal NENs; C) low grade (Grade 1-2) pancreatic NENs; D) High grade (grade 3) gastroenteropancreatic NENs**.** ORR in PD-L1 CPS subgroups were calculated regarding those patients with evaluable CPS score.

Abbreviations: NENs, neuroendocrine neoplasms; GEP: Gastroenteropancreatic; CR, complete response; GI-NET, GI neuroendocrine tumor; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; PD-L1, Programmed Death ligand 1.

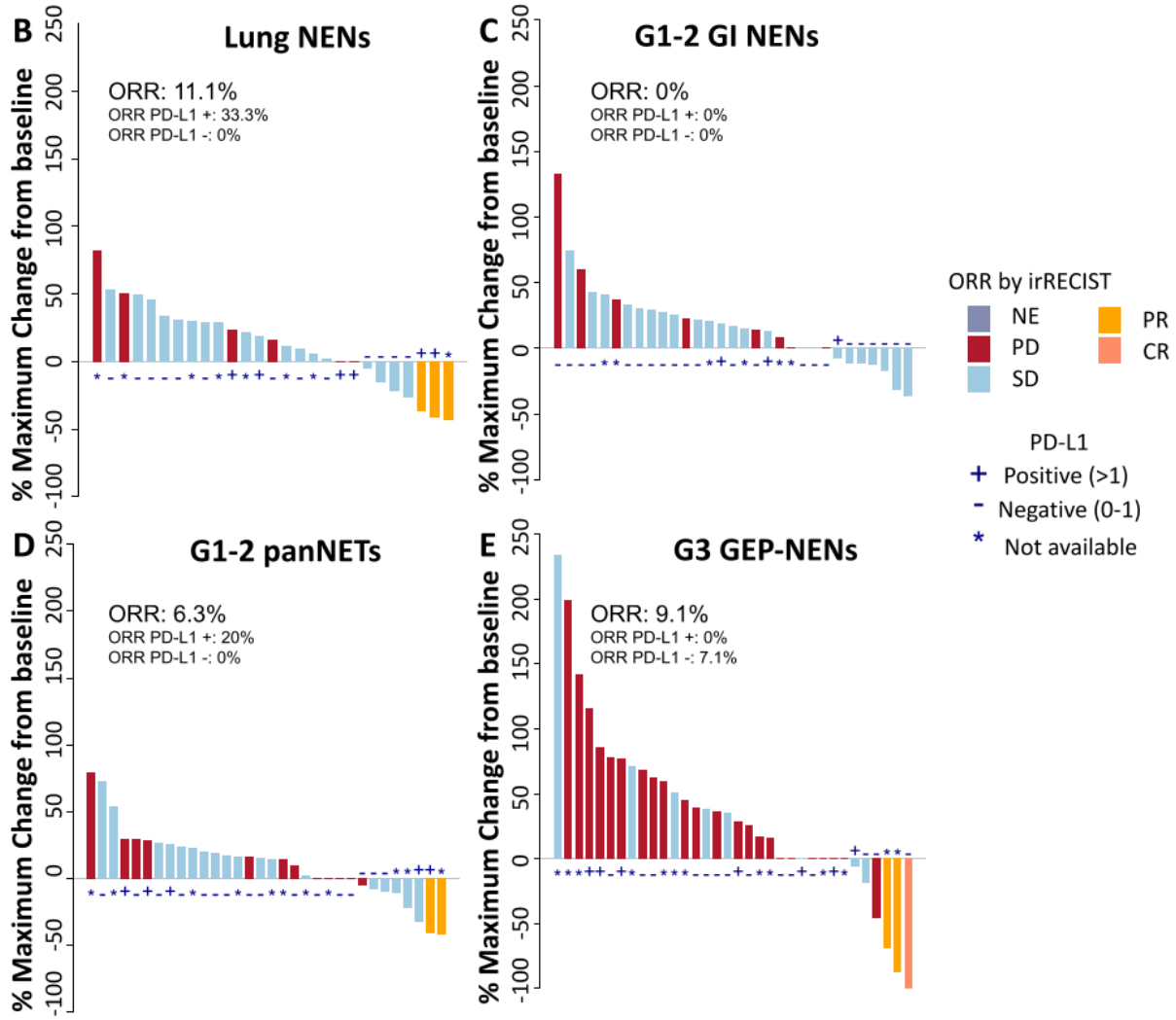

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Figure 3. Tumor size changes by RECIST 1.1. Spider plot showing changes in tumor size from baseline for each patient. Those patients having as their best response a complete response are shown in dark green, those with a partial response in light green, those with stable disease in yellow, and those with progression disease in red. A) Typical / atypical lung carcinoids; B) low grade (Grade 1-2) gastrointestinal NENs; C) low grade (Grade 1-2) pancreatic NENs; D) High grade (grade 3) gastroenteropancreatic NENs.

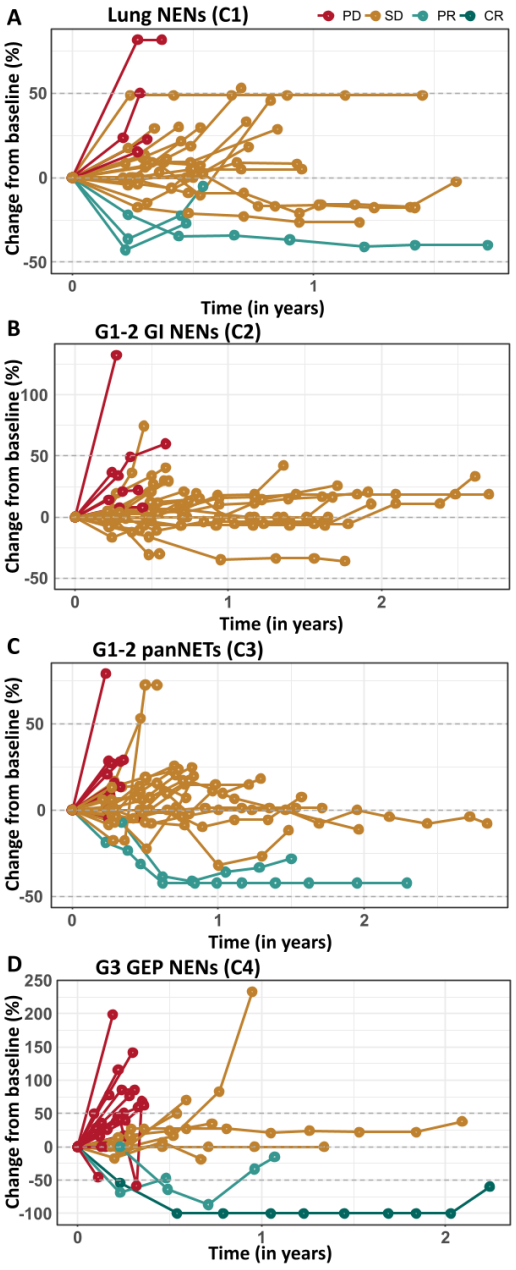

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Figure 4. PFS for each cohort (A), and PFS stratified by PD-L1 CPS status for each cohort (B - E).
Abbreviations: NENs, neuroendocrine neoplasms; PFS, progression free survival.

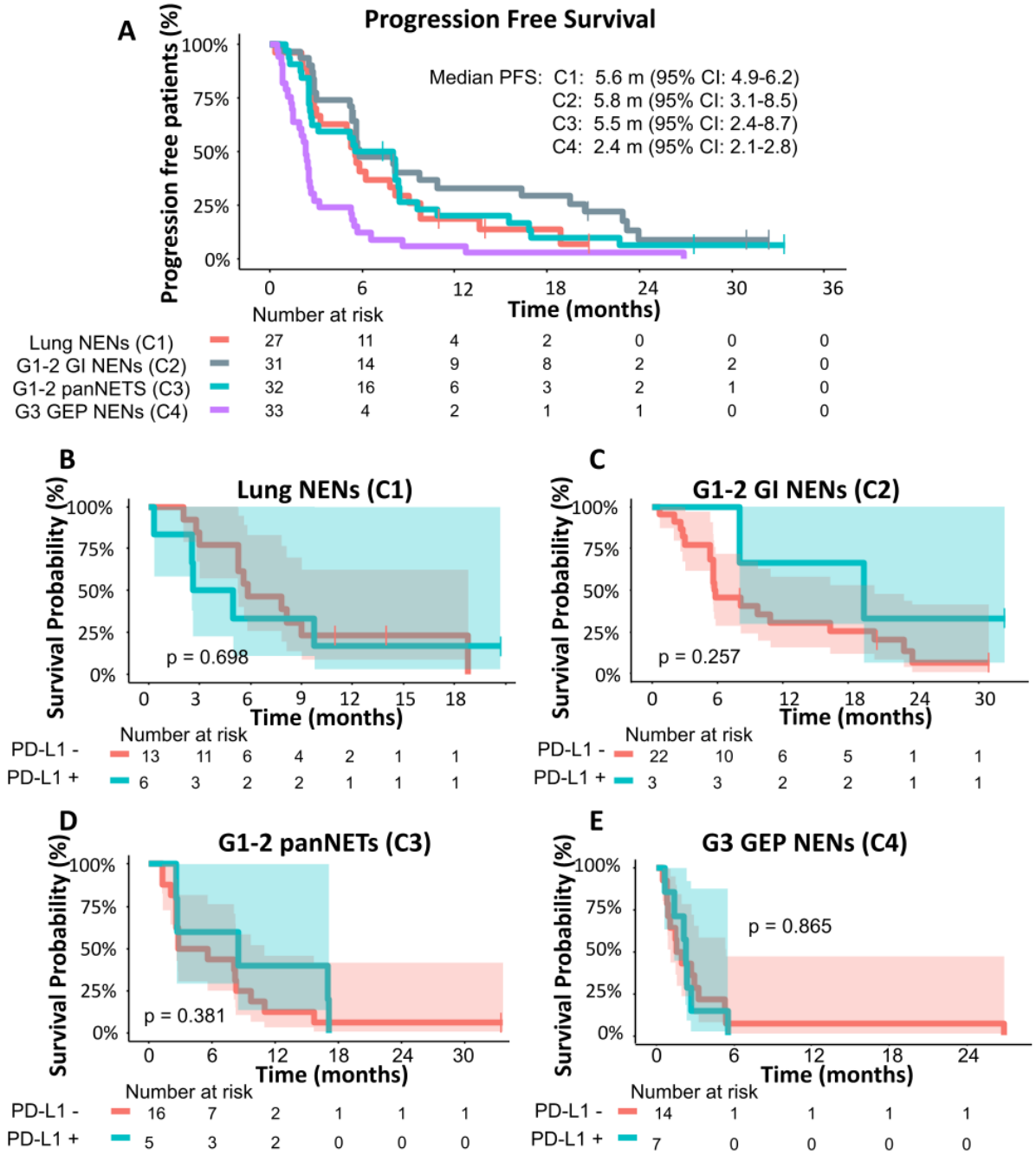

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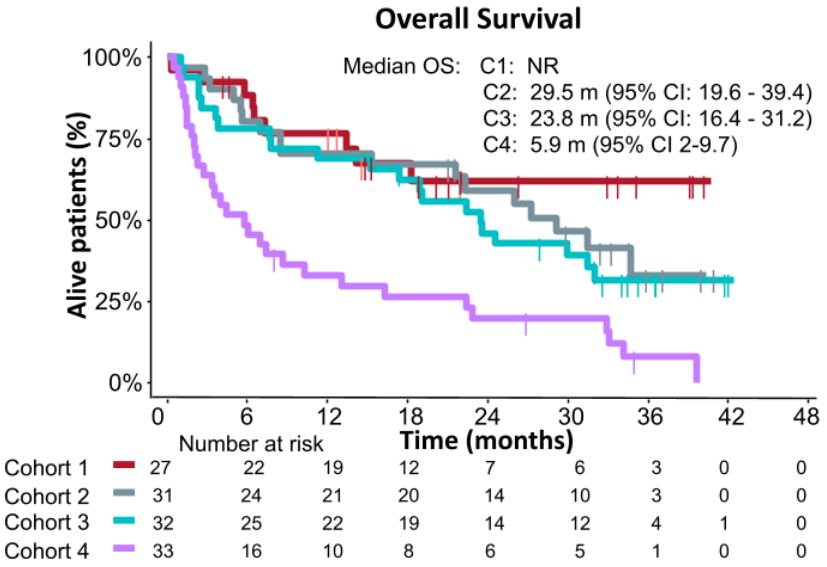
Figure 5. OS for each cohort. Cohort 1, typical or atypical lung carcinoids (red); cohort 2, G1-2 gastrointestinal (gray); cohort 3 G1-2 pancreatic (green); and cohort 4 high grade (grade 3) GEP NENs (purple). Abbreviations: NENs, neuroendocrine neoplasms; OS, overall survival.



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