

World Journal of *Gastroenterology*

World J Gastroenterol 2021 December 21; 27(47): 8040-8200



EDITORIAL

- 8040 Progress in elucidating the relationship between *Helicobacter pylori* infection and intestinal diseases
Fujimori S

FRONTIER

- 8047 Orphan patients with inflammatory bowel disease - when we treat beyond evidence
Privitera G, Pugliese D, Lopetuso LR, Scaldaferrì F, Papa A, Rapaccini GL, Gasbarrini A, Armuzzi A
- 8058 Analogies between medusa and single port surgery in gastroenterology and hepatology: A review
Mittermair C, Weiss HG

EXPERT CONSENSUS

- 8069 Chinese expert consensus on neoadjuvant and conversion therapies for hepatocellular carcinoma
Zhao HT, Cai JQ

REVIEW

- 8081 Present and future management of viral hepatitis
González Grande R, Santaella Leiva I, López Ortega S, Jiménez Pérez M

MINIREVIEWS

- 8103 Artificial intelligence-assisted colonoscopy: A review of current state of practice and research
Taghiakbari M, Mori Y, von Renteln D
- 8123 Immunotherapies for well-differentiated grade 3 gastroenteropancreatic neuroendocrine tumors: A new category in the World Health Organization classification
Xu JX, Wu DH, Ying LW, Hu HG

ORIGINAL ARTICLE**Basic Study**

- 8138 Impact of intrarectal chromofungin treatment on dendritic cells-related markers in different immune compartments in colonic inflammatory conditions
Kapoor K, Eissa N, Tshikudi D, Bernstein CN, Ghia JE
- 8156 Multiparameter magnetic resonance imaging of liver fibrosis in a bile duct ligation mouse model
Liu JY, Ding ZY, Zhou ZY, Dai SZ, Zhang J, Li H, Du Q, Cai YY, Shang QL, Luo YH, Xiao EH

Retrospective Study

- 8166** Disease control and failure patterns of unresectable hepatocellular carcinoma following transarterial radioembolization with yttrium-90 microspheres and with/without sorafenib

Teyateeti A, Mahvash A, Long J, Abdelsalam M, Avritscher R, Kaseb A, Odisio B, Ravizzini G, Surasi D, Teyateeti A, Macapinlac H, Kappadath SC

Observational Study

- 8182** Real-world local recurrence rate after cold polypectomy in colorectal polyps less than 10 mm using propensity score matching

Saito M, Yamamura T, Nakamura M, Maeda K, Sawada T, Ishikawa E, Mizutani Y, Ishikawa T, Kakushima N, Furukawa K, Ohno E, Kawashima H, Ishigami M, Fujishiro M

LETTER TO THE EDITOR

- 8194** Microarray analysis to explore the effect of CXCL12 isoforms in a pancreatic pre-tumor cell model

Miao YD, Wang JT, Tang XL, Mi DH

- 8199** Progress on global hepatitis elimination targets

Waheed Y

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Ki Mun Kang, MD, PhD, Chairman, Professor, Department of Radiation Oncology, College of Medicine, Gyeongsang National University, 79 Gnagnam-ro, Jinju 52727, South Korea. jsk92@gnu.ac.kr

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for WJG as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG’s CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing; **Production Department Director:** Xiang Li; **Editorial Office Director:** Ze-Mao Gong.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

December 21, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Immunotherapies for well-differentiated grade 3 gastroenteropancreatic neuroendocrine tumors: A new category in the World Health Organization classification

Jun-Xi Xu, De-Hao Wu, Li-Wei Ying, Han-Guang Hu

ORCID number: Jun-Xi Xu 0000-0002-7180-5020; De-Hao Wu 0000-0002-1911-5049; Li-Wei Ying 0000-0003-2410-5117; Han-Guang Hu 0000-0002-2330-6569.

Author contributions: Xu JX designed the review, drafted the manuscript, sorted and analyzed the data, and prepared the table; Wu DH and Ying LW assisted in editing the table and contributed to clinical data collection; Hu HG coordinated the design of the outline and critically revised the paper; all authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors have no conflict of interests to report.

Country/Territory of origin: China

Specialty type: Oncology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D

Jun-Xi Xu, Han-Guang Hu, Department of Medical Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, Zhejiang Province, China

De-Hao Wu, Cancer Institute, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, Zhejiang Province, China

Li-Wei Ying, Department of Orthopedic, Taizhou Hospital, Wenzhou Medical University, Linhai 317000, Zhejiang Province, China

Corresponding author: Han-Guang Hu, PhD, Academic Fellow, Associate Chief Physician, Doctor, Professor, Department of Medical Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, No. 88 Jiefang Road, Hangzhou 310009, Zhejiang Province, China. huhanguang@zju.edu.cn

Abstract

According to the 2019 World Health Organization (WHO) classification, well-differentiated grade 3 (G3) gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) are a new category of cancer of the digestive system. G3 GEP-NET research and treatment are not as robust as those of lower grade (G1/2) NETs and poorly differentiated neuroendocrine carcinomas (NECs). Previously, the management of high-grade NETs was mainly based on NEC therapies, as high-grade NETs were classified as NECs under the previous WHO classification. Despite this, G3 GEP-NETs are significantly less responsive to platinum-based chemotherapy regimens than NECs, due to their distinct molecular pathogenesis and course of pathological grade transition. Patients with advanced G3 GEP-NETs, who have progressed or are intolerant to chemotherapy regimens such as capecitabine plus temozolomide, have limited treatment choices. Immunotherapy has helped patients with a variety of cancers attain long-term survival through the use of immune checkpoint inhibitors. Immunotherapies, either alone or in combination with other therapies, do not have a clear function in the treatment of G3 GEP-NETs. Currently, the majority of immunotherapy studies, both prospective and retrospective, do not reliably differentiate G3 GEP-NETs from NECs. By contrast, a significant number of studies include non-GEP neuroendocrine neoplasms (NENs). Therefore, there is an urgent need to summarize and evaluate these data to provide more effective therapeutic approaches for patients with this rare tumor. The purpose of this mini-review was to screen and

Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Received: September 8, 2021

Peer-review started: September 8, 2021

First decision: October 16, 2021

Revised: October 28, 2021

Accepted: November 30, 2021

Article in press: November 30, 2021

Published online: December 21, 2021

P-Reviewer: Ahmed M, Cho JH

S-Editor: Yan JP

L-Editor: Filipodia

P-Editor: Yan JP



summarize information on G3 GEP-NETs from all studies on NENs immunotherapy.

Key Words: Gastrointestinal tract; Pancreas; Immune checkpoint inhibitors; Immunotherapy; Neuroendocrine tumors; Cytotoxic T-lymphocyte-associated protein 4 antigen

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Several evaluations have been published on immunotherapy for neuroendocrine neoplasms. However, this is the first review to specifically focus on the efficacy of different immunotherapy strategies such as immune checkpoint inhibitor (ICI) monotherapy, dual ICI therapy, anti-angiogenesis plus ICI, and chemotherapy combined with ICI for the treatment of advanced well-differentiated high-grade gastroenteropancreatic neuroendocrine tumors.

Citation: Xu JX, Wu DH, Ying LW, Hu HG. Immunotherapies for well-differentiated grade 3 gastroenteropancreatic neuroendocrine tumors: A new category in the World Health Organization classification. *World J Gastroenterol* 2021; 27(47): 8123-8137

URL: <https://www.wjgnet.com/1007-9327/full/v27/i47/8123.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v27.i47.8123>

INTRODUCTION

Neuroendocrine neoplasms (NENs) are rare and indolent diseases that can manifest in any part of the body where peptidergic neurons and neuroendocrine cells are found. About 65% of neoplasms are found in the gastrointestinal (GI) tract and pancreas, making gastroenteropancreatic (GEP)-NENs the most common type of NENs[1]. Due to advancements in early-stage disease detection techniques such as endoscopy and imaging, the incidence of GEP-NENs has significantly increased to an overall incidence of 3.56 per 100000[2]. Based on the 2010 grading system, the World Health Organization (WHO) in 2019 comprehensively considered the importance of the primary site, morphological differentiation, and grading in the classification of GEP-NENs, and expanded the 2017 grading system by proposing a classification framework for all NENs[3]. One of the key updates in the 2019 classification system is that all grade 3 (G3) NENs (with Ki-67 proliferation index > 20%) are classified as either well-differentiated G3 neuroendocrine tumors (NETs) or poorly differentiated neuroendocrine carcinomas (NECs). Although G3 NETs have more inert biological behavior compared to NECs, they have a poorer prognosis compared to G1/2 NETs [4]. Compared to patients with poorly differentiated NECs, well-differentiated G3 NET patients have a considerably longer median overall survival (mOS) (41-99 mo *vs* 17 mo)[5].

G3 NENs account for 13.4% of all digestive system NENs, whereas G3 NETs account for 18%-20% of G3 GEP-NENs[6,7]. In general, although significant progress has been made in the management of GEP-NENs as a whole, the treatment of G3 GEP-NETs, a new WHO category, has not been well studied. Therefore, more tailored treatment strategies are needed for these disorders.

According to WHO 2010 classification criteria, G3 GEP-NETs were categorized as NECs. However, clinical variations between individuals with G3 GEP-NETs and NECs were discovered. For example, platinum-based chemotherapy was frequently employed for the treatment of G3 GEP-NEN patients in the past. Patients with G3 NETs or Ki-67 < 55% (mostly well-differentiated) were significantly less responsive to treatment than those with NEC or Ki-67 ≥ 55% (mostly poorly differentiated). G3 NET and NEC patients have an objective response rate (ORR) of less than 17% and 35%-70%, a median progression-free survival rate (mPFS) of 2.4-4 mo and 5.0 mo, and mOS of 17 mo and 99 mo, respectively[8-10].

Recently, the first prospective Phase II study of capecitabine with temozolomide in patients with high-grade GEP-NEN and Ki-67 index < 55% yielded results contrary to those received platinum plus etoposide. Patients with G3 NET (*n* = 23) responded better to treatment than those with NEC (*n* = 7) in both short-term [ORR 34.8% *vs*

14.3%, $P = 0.393$; disease control rate (DCR) 87.0% *vs* 42.9%, $P = 0.033$] and long-term (mPFS 9.3 mo *vs* 3.5 mo, $P = 0.005$; mOS did not reach *vs* 6.2 mo, $P = 0.004$) evaluations [11]. In addition, a retrospective study showed that the first-line fluoropyrimidine-based regimens with oxaliplatin (FOLFOX/XELOX) also achieved superior results (mPFS of 7.9 mo and mOS of 30 mo) in 34 patients with G3 GEP-NETs[12].

However, there is no established treatment for G3 GEP-NET patients who are insensitive or resistant to chemotherapy. Peptide receptor radionuclide therapy (PRRT) is a promising alternative approach to chemotherapy. In a retrospective cohort study, PRRT was delivered to G3 GEP NEN patients and their response was examined. The study found that ORR was not significantly different across well-differentiated ($n = 60$) and poorly differentiated ($n = 62$) disease subgroups (42% *vs* 43%). However, DCR, mPFS, and mOS were much longer in patients with well-differentiated tumors than those with poorly differentiated cancers (DCR 93% *vs* 68%, mPFS 19 mo *vs* 8 mo, and mOS 44 mo *vs* 19 mo)[13]. Regrettably, this new therapy is only available in a few countries. Therefore, there is an urgent need to compensate for the inadequacies of the aforementioned medications in patients with G3 GEP-NETs.

In recent years, immunotherapy has emerged as a new and intriguing approach for cancer therapy. Cancer cells have the inherent ability to express negative regulatory molecules of immune cells. The cornerstone of immunotherapy in modern oncology aims to improve the ability of the immune system to recognize and kill tumor cells [14]. Currently, this is being achieved through the use of monoclonal antibodies against immune checkpoints such as programmed death-ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Immune checkpoint inhibitors (ICIs), which sit at the forefront of cancer immunotherapy, have revolutionized the management of a variety of solid malignancies. In relation to NENs, immunotherapy has been mainly used to treat lung and skin tumors such as Merkel cell carcinoma, malignant melanoma, and small cell lung cancer (SCLC)[15]. Although an increasing number of clinical trials and retrospective studies are being conducted to investigate the efficacy of ICIs on NENs of the digestive tract, the role of immunotherapy approaches in well-differentiated G3 NETs has not been sufficiently studied.

In this minireview, we briefly describe the overall pathological changes of G3 GEP-NETs and analyze in detail the immunotherapy experience with well-differentiated G3 GEP-NETs from complex investigations.

ROLE OF IMMUNOTHERAPY IN G3 GEP-NETs

A recent systematic review and meta-analysis of 636 NEN patients treated with ICIs reported an ORR of 10% [95% confidence interval (CI): 6%-15%, $I^2 = 67%$, $P < 0.1$], a total DCR of 42%, a mPFS of 4.1 mo (95%CI: 2.6-5.4; $I^2 = 96%$, $P < 0.1$), and a mOS of 11 mo (95%CI: 4.8-21.1; $I^2 = 98%$, $P < 0.1$)[16]. This demonstrated the overall effectiveness of ICIs in treating NEN patients. Among the NEN study subjects, about 37% were patients with NENs originating from the lung or other unknown sites and only 13.4% were patients who had G3 NETs. However, the study did not include a separate subgroup of G3 GEP-NET patients in its analysis. Previous studies have shown that G3 NETs can share a common pathogenesis with G1-2 NETs[17]. Moreover, more than half of G1-2 pancreatic NETs (pNETs) developed progressively into G3 pNENs over time[18]. Some researchers have even speculated that high-grade pNET may develop from the initial low- and medium-grade NET, while pNEC may develop from pancreatic ductal adenocarcinoma[19,20]. Therefore, the response of lower grade NETs to immunotherapy may have some implications for the treatment of G3 NETs. Other aspects that may influence the immunotherapy choices for G3 GEP-NETs include the presence of predictive biomarkers for ICIs in tumors with high proliferative activity as well as changes in pathological grade over time.

Table 1 summarizes the clinical trials of immunotherapy in GEP-NENs. Below, we presented data from clinical trials and retrospective studies that may have included cases with G3 GEP-NETs. Additionally, we analyzed the data to determine the efficacy of different immunotherapy strategies such as PD-1/PD-L1 inhibitors as a monotherapy or in combination with CTLA-4 inhibitors, anti-angiogenesis, and chemotherapy in the management of these rare diseases.

ICIs monotherapy

Pembrolizumab is the most extensively investigated immunotherapy for NENs. For example, phase Ib (KEYNOTE-28) and phase II (KEYNOTE-158) clinical trials were

Table 1 Clinical trials related to gastroenteropancreatic neuroendocrine tumors

ClinicalTrials.gov identifier	Intervention	Study phase	Trial name	Primary outcome	Estimated/actual enrollment, <i>n</i>	Estimated/actual date	Trial status	Medical condition related to advanced NENs	Reported assessable n of NENs
NCT02054806[21]	Pembrolizumab	Ib	Phase Ib study of pembrolizumab (MK-3475) in subjects with select advanced solid tumors (MK-3475-028/KEYNOTE-028)	ORR	477	April 30, 2021	Completed	pNETs: PD-L1 (+), well or moderately differentiated	16 pNETs
NCT02628067[22]	Pembrolizumab	II	A clinical trial of pembrolizumab (MK-3475) evaluating predictive biomarkers in subjects with advanced solid tumors (KEYNOTE-158)	ORR	1595	June 18, 2026	Recruiting	NETs: Well or moderately differentiated	107 NETs: Lung, appendix, small intestine, colon, rectum, or pan origin
NCT02939651[23]	Pembrolizumab	II	A phase 2, open-label study of pembrolizumab monotherapy in patients with metastatic high grade neuroendocrine tumors	ORR	21	March 2020	Completed	G3 NENs: Ki-67 > 20%, poorly or well-differentiated, failed for platinum based chemotherapy, excluding MCC, large/small cell NENs of lung/thymus origin	29 G3 NENs: 19 NECs, 9 G3 NET, 14 Ki-67 ≤ 50%, 12 Ki-67 > 50%, 10 pan, 14 GI, 5 unknown origin
NCT03136055[24, 48]	Part A: pembrolizumab alone; Part B: Pembrolizumab + chemotherapy	II	A pilot study of pembrolizumab-based therapy in previously treated high grade neuroendocrine carcinomas	ORR	36	May 31, 2023	Active, not recruiting	EP-PDNECs: Failed for first-line systemic therapy, excluding MCC or well differentiated G3 NET	Part A: 13 EP-PDNECs; Part B: 22 EP-PDNEC
NCT03190213	Pembrolizumab	II	Pembrolizumab for the treatment of recurrent high grade neuroendocrine carcinoma (Pembro NEC)	ORR (irRECIST)	6	March 11, 2019	Terminated	G3 NENs: Failed for platinum-based regimen or temozolomide-based regimen. excluding lung origin	6 G3 NENs
NCT02955069[25]	Spartalizumab	II	An open label phase II study to evaluate the efficacy and safety of PDR001 in patients with advanced or metastatic, well-differentiated, non-functional neuroendocrine tumors of pancreatic, gastrointestinal (GI), or thoracic origin or poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC), that have progressed on prior treatment	ORR	116	May 13, 2020	Completed	NENs: Exclude G3 NETs and include G1/2 NET (non-functional, GEP or thoracic origin, failed to prior treatment) and GEP-NEC (progressed on or after one prior chemotherapy regimen)	99 NETs: 30 thoracic, 32 GI-NET, 33 pNET; 21 GEP-NEC
NCT03167853[30]	Toripalimab	Ib	Phase Ib study of safety and efficacy of recombinant humanized anti-PD-1 monoclonal antibody for patients with advanced neuroendocrine tumors following failure of first-line	ORR	40	May 11, 2019	Completed	NENs: Ki-67 ≥ 10%, nonfunctional NENs, well- or poorly-differentiated, failed for first line therapy	40 NENs: 8 well-differentiated, 32 poorly-differentiated
NCT03352934[26]	Avelumab	II	A phase II, open-label, multicenter trial to	DCR	60	January 2024	Active, not	G3 NENs: after first-line	29 G3 NENs: 16 NEC

			investigate the clinical activity and safety of avelumab in patients with advanced, metastatic high grade neuroendocrine carcinomas NEC G3 (WHO 2010) progressive after chemotherapy (AveNEC)				recruiting	chemotherapy, excluding MCC, SCLC	and 11 G3 NETs, 12 pan, 5 GI, 9 other origin)
NCT03278405[58]	Avelumab	Ila	A pilot study of avelumab in unresectable/metastatic, progressive, poorly differentiated grade 3 neuroendocrine carcinomas (NET001)	ORR	10	March 12, 2020	Completed	NECs: Poorly-differentiated, GI or lung origin, have received 0-2 prior lines of systemic therapy, excluding MANEC	10 NECs: 9 GI and 1 lung
NCT03278379[28]	Avelumab	II	A phase II study of avelumab in unresectable/metastatic, progressive grade 2-3 neuroendocrine tumors (NET-002)	ORR	17	September 20, 2021	Active, not recruiting	G2-3 NETs: GEP or lung, received 0-2 prior lines of therapy (excluding SSAs), excluding G1 NET, NEC and MANEC	17 G2-3 NETs (12 GEP, 5 lung)
NCT03147404	Avelumab	II	Phase II study of avelumab in metastatic gastropancreatic (GEP) neuroendocrine carcinoma (NEC, WHO Grade 3) as second-line treatment after failing to etoposide + cisplatin: integration of genomic analysis to identify predictive molecular subtypes (MS100070-0177)	Best response	14	July 22, 2019	Completed	G3 GEP-NECs: Second-line treatment after failing to etoposide + cisplatin	-
NCT03879057[39]	Toripalimab + surufatinib	I	Phase I trial evaluating the safety, tolerability, pharmacokinetics, and efficacy of surufatinib combined with JS001 in patients with advanced solid tumors	AEs, MTD	24	December 20, 2021	Recruiting	NENs: G1-3 NET, NEC	18 NENs:11 NECs,4 G2 NETs; 4 G3 NETs, 12 GI,4 pan, 1 lung
NCT04169672[40]	Toripalimab + surufatinib	II	A phase II, open-label, single-arm, multi-center study of the efficacy and safety of surufatinib combined with toripalimab in patients with advanced solid tumors	AEs, ORR	200	February 28, 2022	Recruiting	NECs: Refractory to first-line chemotherapy	20 NECs
NCT03475953	Avelumab + regorafenib	I/II	A phase I/II study of regorafenib plus avelumab in solid tumors (REGOMUNE)	Phase I: Recommended dose of regorafenib; Phase II: ORR, PFS	482	May 2022	Recruiting	G2/3 GEP-NETs	-
NCT03290079	Pembrolizumab + lenvatinib	II	Phase II study of pembrolizumab and lenvatinib in advanced well-differentiated neuroendocrine tumors	ORR	35	December 2023	Recruiting	NETs: Well-differentiated, lung, thymus, small bowel or colon origin, including unknown primary, excluding pNENs and poorly differentiated NECs	-
NCT04579757	Surufatinib + tislelizumab	Ib/II	An open-label phase Ib/II study of	DLT, ORR	120	April 30, 2023	Recruiting	G1/2 NETs: Thoracic or	-

			surufatinib in combination with tislelizumab in subjects with advanced solid tumors				GEP origins, have progressed on at least one line of standard therapy		
NCT04207463	AK105 + anlotinib	II	A phase II, open, single-arm, multi-cohort, multicenter study of anlotinib and AK105 (anti-PD-1) injection in subjects with gastrointestinal tumors, urinary system tumors, neuroendocrine tumors	ORR	150	May 30, 2021	Recruiting	G1/2 GEP-NETs	-
NCT03074513[41]	Atezolizumab + bevacizumab	II	A phase II, single-arm open-label study of the combination of atezolizumab and bevacizumab in rare solid tumors	ORR	164	March 31, 2021	Active, not recruiting	G1/2 NETs: pNET cohort and epNET cohort containing typical or atypical carcinoid if originating in lung	20 G1/2 pNETs, 20 G1/2 epNETs
NCT02923934[45]	Nivolumab + ipilimumab	II	A phase II clinical trial evaluating ipilimumab and nivolumab in combination for the treatment of rare gastrointestinal, neuro-endocrine and gynaecological cancers (CA209-538)	CBR	120	December 2023	Active, not recruiting	NENs: G1-3 NETs, NECs, GEP or lung origin	10 GEP-NENs: 7 pNENs (3 G3 pNETs, 2 pNECs, 2 G2 pNETs); 3 GI-NENs (1 gastro-oesophageal junction NEC, 1 colonic NECs, 1 G1 gastric NET)
NCT02834013[15, 46]	Nivolumab + ipilimumab	II	A prospective, open-label, multicenter phase II basket clinical trial of ipilimumab plus nivolumab across multiple rare tumor cohorts (DART)	ORR	818	August 1, 2021	Recruiting	SWOG 1609 cohort: Refractory epNENs. G3 NETs were included in G3 NECs. SWOG S1609 cohort: Dedicated cohort include G3 NENs	SWOG 1609 cohort: 32 epNENs (18 G3, 10 G2, 4 G1, 15 GI, 6 Lung). S1609 cohort: 19 G3 NENs (2 G3 NETs, 11 NEC, 6 unknown differentiation status)
NCT04969887	Nivolumab + ipilimumab	II	Ipilimumab and nivolumab combination therapy in patients with selected immunotherapy sensitive advanced rare cancers (MOST-CIRCUIT)	CBR	240	December 2024	Not yet recruiting	NECs and G3 NETs independent of primary site, excluding SCLC	-
NCT03591731	Nivolumab alone or nivolumab + ipilimumab	II	A GCO trial exploring the efficacy and safety of nivolumab monotherapy or nivolumab plus ipilimumab in pre-treated patients with advanced, refractory pulmonary or gastroenteropancreatic poorly differentiated neuroendocrine tumors (NECs) (NIPINEC)	ORR	180	September 2023	Recruiting	NECs: Poorly differentiated, refractory, pulmonary or GEP, excluding SCLC	-
NCT03095274[47]	Tremelimumab + durvalumab	II	A phase II study of durvalumab (MEDI4736) plus tremelimumab for the treatment of patients with advanced neuroendocrine neoplasms of gastroenteropancreatic or lung origin (DUNE) (GETNE 1601)	Cohort 1-3: CBR at 9 m; Cohort 4: OS at 9 mo	126	July 2021	Recruiting	G1/G2 NETs of GEP and lung, and G3 of GEP or unknown primary site (excluding lung primaries) after progression to standard therapies	123 NENs (Cohort 1: 27 typical/atypical lung carcinoid; Cohort 2: 31 G1/2 GI-NENs; Cohort 3: 32 G1/2 pNENs; Cohort 4: 33 G3 NEN of GEP or unknown primary site)

NCT04079712	Nivolumab + ipilimumab + cabozantinib	II	A phase 2 study of XL184 (Cabozantinib) in combination with nivolumab and ipilimumab for the treatment of poorly differentiated neuroendocrine carcinomas	ORR	30	October 1, 2021	Recruiting	NECs: All variations of poorly differentiated NECs (small cell, large cell and mixed cells) are eligible, excluding SCLC and MCC. Failure of only one line of prior systemic cancer treatment	-
NCT03728361[49]	Nivolumab + temozolomide	II	A phase II, multi-cohort trial of combination nivolumab and temozolomide in recurrent/refractory small-cell lung cancer and advanced neuroendocrine tumors	ORR	55	December 31, 2021	Active, not recruiting	NENs: Any grade or primary site	12 NENs: 1 G1, 8 G2, 3 G3
NCT03980925	Nivolumab + platinum-doublet chemotherapy	II	A phase II study of platinum-doublet chemotherapy in combination with nivolumab as first-line treatment in subjects with unresectable, locally advanced or metastatic G3 neuroendocrine neoplasms (NENs) of the gastroenteropancreatic (GEP) tract or of unknown (UK) origin (GETNE-T1913)	OS at 12 mo	38	December 2022	Recruiting	G3 NENs: GEP or unknown primary site	-
NCT03365791[59]	Spartalizumab + LAG525	II	Modular phase 2 study to link combination immune-therapy to patients with advanced solid and hematologic malignancies. Module 9: PDR001 plus LAG525 for patients with advanced solid and hematologic malignancies	CBR at 24 wk	76	September 17, 2020	Completed	NETs: Well-differentiated, relapsed and/or refractory to available standard of care therapies	7 NETs
NCT03043664[60]	Pembrolizumab + lanreotide depot	Ib/II	Phase Ib/II study of pembrolizumab with lanreotide depot for gastroenteropancreatic neuroendocrine tumors (PLANET)	ORR	22	September 1, 2021	Active, not recruiting	G1-2 GEP-NETs: Had progressed on a prior SSA	22 G1/2 GEP-NETs (14 GI, 8 pan)
NCT04525638	Nivolumab + ¹⁷⁷ Lu-DOTATATE	II	A phase II single arm trial evaluating the preliminary efficacy of the combination of ¹⁷⁷ Lu-DOTATATE and nivolumab in grade 3 well-differentiated neuroendocrine tumours (NET) or poorly differentiated neuroendocrine carcinomas (NEC)	ORR	30	September 30, 2024	Recruiting	G3 NENs: GEP or unknown primary site, well-differentiated or poorly-differentiated.	-
NCT04701307	Dostarlimab + niraparib	II	Niraparib (PARP Inhibitor) plus dostarlimab (Anti-PD1) for small cell lung cancer (SCLC) and other high-grade neuroendocrine carcinomas (NEC)	6 mo PFS, 3 mo ORR	48	May 30, 2025	Recruiting	G3 NECs: SCLC (Cohort 1) and other G3 NECs (Cohort 2), had at least one prior line of systemic therapy, excluding prostate origin	-
NCT03457948	Group I: Pembrolizumab + ¹⁷⁷ Lu DOTATATE; Group II: Pembrolizumab + TAE; Group III: Pembrolizumab + ⁹⁰ Yttrium- Microsphere Radioembolization	II	A pilot study of pembrolizumab and liver-directed therapy or peptide receptor radionuclide therapy for patients with well-differentiated neuroendocrine tumors and symptomatic and/or progressive metastases	ORR	32	March 31, 2024	Recruiting	G1-3 NETs: Well-differentiated, any primary site and unknown primary site, have liver metastases	-

NCT03879694	SVN53-67/M57-KLH peptide vaccine (SurVaxM) +Octreotide	I	A phase I study of safety and immunogenicity of Survivin Long Peptide Vaccine (SurVaxM) in patients with metastatic neuroendocrine tumors (NETs)	AEs	10	June 13, 2024	Recruiting	NETs: GEP or lung origin, positive for survivin	-
NCT04166006	Dendritic cells loaded with autologous tumour (DC vaccine) + IL-2	II	A phase II study on adjuvant vaccination with dendritic cells loaded with autologous tumor homogenate in resected stage iv rare cancers: Head & neck (H & N), neuroendocrine tumors (NET) and soft tissue sarcoma (STS)	Treatment-Emergent AEs	51	December 2026	Recruiting	NET: Stage IV	-

AE: Adverse event; CBR: Clinical benefit rate; DCR: Disease control rate; DLT: Dose-limiting toxicity; EP-PDNECs: Extrapulmonary poorly differentiated neuroendocrine carcinomas; ep: Extra-pancreatic; G1, 2, 3: Grade 1, 2, 3; GEP: Gastroenteropancreatic; GI: Gastrointestinal; irRECIST: Immune-related Response Evaluation Criteria in Solid Tumors; MANEC: Mixed adenoneuroendocrine carcinomas; MCC: Merkel cell carcinoma; MTD: Maximum tolerated dose; NECs: Neuroendocrine carcinomas; NENs: Neuroendocrine neoplasms; NETs: Neuroendocrine tumors; ORR: Objective response rate; OS: Overall survival; p: Pancreatic; pan: Pancreas origin; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; SCLC: Small cell lung cancer; WHO: World Health Organization.

conducted to evaluate pembrolizumab monotherapy in patients with moderately or well-differentiated NETs. In these two studies, no data on tumor grade and Ki-67 index were collected. The results of the KEYNOTE-28 trial showed an ORR of 6.3% in pNETs[21]. The preliminary results of the KEYNOTE-158 study showed that mixed NETs had an ORR of 3.7% and that all reactive tumors were PD-L1-negative[22]. In addition, two prospective randomized phase II trials were performed to evaluate pembrolizumab in 19 patients with NECs and 9 with G3 NETs. There were no responses to pembrolizumab in patients with GI tract or pancreatic diseases[23]. In a trial of 14 patients with extrapulmonary poorly differentiated NECs, only 1 patient achieved complete remission (CR) (ORR 7%) following pembrolizumab monotherapy [24]. From the abovementioned studies, it can be concluded that pembrolizumab alone has a very limited curative effect on the GEP-NENs independent of their proliferative activity or differentiation. The only clinical trial (NCT02955069) of spartalizumab, a PD-1 inhibitor, for the treatment of NENs excluded patients with G3 NETs and achieved low efficacy comparable to pembrolizumab[25]. Avelumab is the only PD-L1 inhibitor used as a single drug in prospective clinical trials for GEP-NENs. Four phase II clinical trials (NCT03352934[26], NCT03278405[27], NCT03278379[28], and NCT03147404) were conducted to evaluate avelumab in patients with G2/3 NETs or NEC. The trials revealed that none of the patients achieved an objective response to avelumab treatment. In addition, none of the 3 G3 NET patients analyzed in a retrospective study from the Mayo Clinic exhibited an objective response to ICI (pembrolizumab, nivolumab, or atezolizumab) monotherapy[29].

Toripalimab (JS001) is a humanized PD-1 IgG4 monoclonal antibody developed in China. In a phase Ib study (NCT03167853) involving 40 NEN patients with Ki-67 ≥ 10%, toripalimab showed moderate efficacy in both well-differentiated NETs and poorly differentiated NECs (ORR: 25.0% vs 18.7% per RECIST 1.1, 25.0% vs 25.0% per irRECIST)[30]. This suggests that toripalimab may be the most effective ICI

monotherapy currently available for NENs, including G3 NETs. The study also found that patients with PD-L1 expression $\geq 10\%$ or with high tumor mutational burden (TMB) had a better ORR than patients with PD-L1 $< 10\%$ (50.0% *vs* 10.7%, $P = 0.019$) or with low TMB (75.0% *vs* 16.1%, $P = 0.03$)[30].

Anti-angiogenesis combined with ICIs

NENs from different tissues are highly vascularized and express a variety of growth factors including vascular endothelial growth factor (VEGF), platelet-derived growth factor, basic fibroblast growth factor, insulin-like growth factor 1, and transforming growth factor- α/β [31]. The high exposure and activation of VEGFs prevent the immune system from recognizing and killing cancer cells killing tumor cells[32,33].

The hallmark of angiogenesis is the uncontrolled development of new vessels from adjacent normal tissues. This results in a network of immature microvessels characterized by structural and functional abnormalities. The normalizing vascular structure can be achieved with antiangiogenic drugs, including large-molecule monoclonal antibodies and small-molecule tyrosine kinase inhibitors. This results in the activation of adhesion molecules and chemokines that recruit and attract cytotoxic T cells and reduce the entry of regulatory T cells. Moreover, it contributes to immune cell mobilization[34,35].

Surufatinib is a small molecule inhibitor that mainly targets VEGF-1, 2, 3 (VEGFR-1, 2, 3), fibroblast growth factor receptor-1, and colony-stimulating factor-1 receptor (CSF-1R). Blocking of CSF-1R can reduce the polarization of tumor-associated macrophages to the M2 type that participates in immunosuppression and promotes tumor growth[36,37]. Two randomized, double-blind phase III clinical trials (SANET-ep and SANET-p) were carried out to evaluate surufatinib *vs* placebo in Chinese patients with G1-2 NETs. The results indicated that surufatinib can significantly prolong PFS in patients with advanced pancreatic and non-pancreatic G1-2 NETs compared with placebo[37,38]. At present, a phase I trial and a phase II trial of surufatinib combined with toripalimab on patients with NENs are underway. In a phase I clinical trial (NCT03879057), as of 2020-1-20, PR occurred in G1/2 NET (2/4) and NECs (2/11) patients; however, none of the 4 patients with G3 NETs achieved disease remission[39], which may be attributed to the small sample size of patients with G3NETs. In the phase II trial (NCT04169672), 20 evaluable patients with NECs and refractory to first-line chemotherapy achieved a moderate ORR of 20% and a DCR of 70%[40]. However, no data for well-differentiated NETs have been reported. In addition, two prospective studies involving G3 GEP-NETs patients are currently recruiting. In one of the trials, the intervention is avelumab plus regorafenib, while in the other study, the intervention is pembrolizumab plus lenvatinib. The studies are expected to be completed in May 2022 and December 2023, respectively. The combination treatment of atezolizumab and bevacizumab in a phase II basket trial (NCT03074513) showed moderate clinical activity and good tolerance in G1-2 pNETs and extra-pNETs (ORR 20% and 15%, respectively) patients with prior therapy[41]. However, the data of G3 NETs have not been reported either.

Given the favorable preliminary results in patients with G1-2 NETs and NECs, researchers might be optimistic about the combination therapy's effectiveness in patients with G3 NETs.

Dual ICI therapy

The United States Food and Drug Administration has approved ipilimumab (anti-CTLA-4) combined with nivolumab (anti-PD-1) (N+I) for melanoma, metastatic renal cell carcinoma, advanced hepatocellular carcinoma, and previously untreated unresectable malignant pleural mesothelioma[42-44]. Response rates with this combination are higher compared to single-agent anti-PD-1 therapy. For NENs, a phase II clinical trial (CA209-538) of N+I demonstrated a moderate overall ORR of 24%, especially in patients with G3 NENs and atypical bronchial carcinoid[45]. In the study, 7 patients with pNENs and 3 with GI-NENs achieved an ORR of 43% and 33.3%, respectively. All responders had a high-grade disease. It is worth noting that 2 of the 3 patients with G3 pNET achieved an objective response. This result is a breakthrough in the application of ICIs in the treatment of G3 GEP-NET. Currently, a phase II study (NCT04969887) on evaluation of N+I in patients with immunotherapy-sensitive cancers including NECs and G3 NETs from CA209-538 has been registered and is expected to be completed in October 2024.

Another phase II basket study of N+I for the treatment of rare tumors called SWOG DART (NCT02834013) was recently reported. In one cohort, 32 patients with epNENs (excluding SCLC, about 50% have GI-NENs) had a significantly higher response rate for high-grade neoplasms than for middle/low-grade neoplasms (ORR 44% *vs* 0%, $P =$

0.004) with no difference in overall ORR between the different primary origins[15]. Based on the results of the cohort, a second and dedicated cohort of 19 individuals with G3 NENs was explored[46]. Although all patients were microsatellite-stable, the results of the cohort revealed a moderate ORR of 26%. Unfortunately, none of the above cohorts performed an analysis of G3 NENs according to differentiation. A similar dilemma existed in a retrospective study at Moffet Cancer Center and the Mayo Clinic, where G3 NEN patients achieved an ORR of 14.75%. Therefore, determining the efficacy of N+I in the treatment of well-differentiated G3 GEP-NETs is challenging.

Durvalumab (anti-PD-L1) in combination with tremelimumab (anti-CTLA-4) (D+T) is another dual ICI therapy that has been studied for advanced NENs of GEP or lung origin. The initial results of DUNE, a prospective phase II multi-cohort study, were presented at the 2020 ESMO Annual meeting[47]. Cohort 4 consisting of 33 G3 GEP-NENs achieved an ORR of 9.1%, and the clinical benefit rate of 36.1% at 9-mo paved the way for a phase III clinical trial of D+T. Regrettably, comparable to N+I, no independent examination of patients with well-differentiated tumors was conducted, although the efficacy of G3 was higher than that of G1-2.

The above results suggest that dual ICIs have moderate overall efficacy in patients with advanced G3 GEP-NENs. Comparatively, the N+I regimen appears to have a greater response rate than D+T. The success of these therapies, however, must be demonstrated in a large number of patients with well-differentiated G3 GEP-NETs.

Chemotherapy combined with ICI

Current research on chemotherapy combined with ICIs, in the field of GEP-NENs, has a small sample size and the majority of them include previously treated NECs. The ORRs vary from 9% for pembrolizumab plus dealers' choice chemotherapy to 36% for nivolumab plus temozolomide[29,48,49]. Since most NEC patients are sensitive to chemotherapy, it is necessary to compare the above results with the data of chemotherapy alone as a second- or later-line treatment option. This comparison will establish whether NEC patients can significantly benefit from the above combination therapy. As previously described, G3 NETs are insensitive to platinum-based chemotherapy. Unfortunately, G3 GEP-NET, as a well-differentiated tumor with high proliferative activity, has not been specifically included in any prospective clinical trials for chemotherapy combined with ICI.

Other immunotherapies

Immunotherapies currently being investigated in prospective clinical trials related to G3 GEP-NET include classic PD-1 inhibitors combined with other therapies such as LAG525 (LAG-3 inhibitor), ¹⁷⁷Lu-DOTATATE (PRRT), and liver-directed therapies (Transarterial Embolization or ⁹⁰Yttrium Microsphere Radioembolization). In addition, the immune tumor vaccines Survivin Long Peptide Vaccine (SurVaxM) and Dendritic Cells Loaded with Autologous Tumor Homogenate (DC vaccine) have entered phase I and phase II clinical trials, respectively. Both vaccines are currently at the subject recruitment stage.

Predictive biomarkers for immunotherapies

The potential of a given patient with G3 GEP-NET to respond to immunotherapies is still largely unknown. NETs can be considered as immunologically "cold" due to their lack of immunoactive cellular components, low tumor antigens, *etc.*[50,51].

Immunohistochemical assessment of PD-L1 expression and its role in predicting response to ICIs is an incredibly hot topic. However, in the KEYNOTE-28 study, pNETs with positive PD-L1 expression achieved a low ORR of 6.3%[21]. In the KEYNOTE-158 study, all 4 GEP-NET patients who achieved PR had negative PD-L1 expression[22]. Besides, in a joint analysis of two prospective, non-randomized trials, no difference in DCR, PFS, or OS was observed between the PD-L1-negative and PD-L1-positive groups with G3 NENs[23]. In contrast, in the phase Ib trial of toripalimab in the treatment of patients with NENs (Ki-67 \geq 10%) described above, patients with PD-L1 expression \geq 10% had better ORR than those with PD-L1 < 10% (50.0% *vs* 10.7%, $P = 0.019$)[30]. Therefore, it appears that considering merely the negative or positive expression of PD-L1 is insufficient for identifying GEP-NET patients who may benefit from ICIs and that quantifying PD-L1 expression appears to be more significant. Furthermore, only 10% of tumors expressed PD-L1 in a large cohort of 136 patients with G3 GEP-NENs and those tumoral cells with positive PD-L1 were all in poorly differentiated cases[52]. Therefore, it is necessary to combine PD-L1 with other predictive biomarkers to better predict the population that may benefit from immuno-

therapy.

For other biomarkers, both high TMB (TMB-H) and microsatellite instability-high (MSI-H)/deficient mismatch repair protein (dMMR) are independent adverse prognostic factors for NENs[53] and also have an important predictive value. Wang *et al*[54] reported that 50% of the 18 Chinese patients with NETs had TMB-H. In a NET cohort analyzed by Patel *et al*[15], found no difference in the PD-L1 positivity rate between G3 and G1/G2 tumors, while the TMB-H rate was significantly higher in G3 NENs independent of tumor origin. Large samples of clinical and genomic data demonstrated that TMB-H was associated with increased survival in patients treated with ICI across various cancer types[55]. Duan *et al*[56] discovered that half of pNEN patients had decreased expression of MMR, another important biomarker. Venizelos *et al*[57] recently reported that MSI occurred in only 5.3% (8/152) of GEP-NEC patients and 3.4% (1/29) of G3 GEP-NET patients.

Pre-treatment assessment of one or more of these biomarkers provides a new perspective for screening good responders to immunotherapy.

CONCLUSION

In this minireview, data from prospective clinical trials and retrospective studies on the role of immunotherapies on G3 GEP-NET has been screened and reviewed. For ICI monotherapy, the efficacy of pembrolizumab, spartalizumab, and avelumab on G3 GEP-NETs is very limited. Only toripalimab has shown a moderate clinical activity on NENs with Ki-67 $\geq 10\%$, PD-L1 expression $\geq 10\%$, or high TMB. In addition, the ORR of well-differentiated tumors treated with toripalimab was slightly better than that of poorly differentiated cancers. Toripalimab and surufatinib therapy did not cause disease remission in 4 patients with G3 NETs. However, the treatment did not prevent remission in NEC and G1-2 NETs. Therefore, these regimens could potentially be effective in the treatment of G3 GEP-NETs if a large number of subjects are included. In other studies, the N+I therapy achieved PD in 2 of 3 patients with G3 NET as well as moderate efficacy in high-grade NENs. These results suggest that N+I may represent an extremely promising treatment option for G3 NET.

At present, all clinical trials investigating G3 GEP-NET are either phase I or phase II studies with small sample sizes. In this study, several challenges were encountered when collecting and evaluating data on the efficacy of immunotherapies for G3 GEP-NETs. According to the 2010 WHO classification, the inclusion of high-grade NETs in studies of NECs, the lack of Ki-67 index data in well-differentiated tumors, and the inclusion of tumors derived from lung, esophageal or unknown tissue all contribute to significant heterogeneity in reported results. Additionally, the review mainly focuses on the ORR to evaluate the potential role of immunotherapies in the treatment of G3 NETs. This is because the majority of prospective studies are ongoing and the survival data are in their infancy. Therefore, it is necessary to conduct prospective clinical trials with a large sample size of pathologically confirmed G3 GEP-NETs to evaluate the efficacy of the above immunotherapies. Besides, referencing data from important biomarkers facilitates the screening of patients who may benefit.

ACKNOWLEDGEMENTS

The authors express their gratitude to the scholars who have conducted prospective and retrospective studies on immunotherapies in the treatment of NENs.

REFERENCES

- 1 **Oronsky B**, Ma PC, Morgensztern D, Carter CA. Nothing But NET: A Review of Neuroendocrine Tumors and Carcinomas. *Neoplasia* 2017; **19**: 991-1002 [PMID: 29091800 DOI: 10.1016/j.neo.2017.09.002]
- 2 **Dasari A**, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 2017; **3**: 1335-1342 [PMID: 28448665 DOI: 10.1001/jamaoncol.2017.0589]
- 3 **Rindi G**, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, Fernandez-Cuesta L, Klöppel G, McCluggage WG, Moch H, Ohgaki H, Rakha EA, Reed NS, Rous BA, Sasano H, Scarpa A, Scazecz JY, Travis WD, Tallini G, Trouillas J, van Krieken JH, Cree IA. A common classification framework for neuroendocrine neoplasms: an

- International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol* 2018; **31**: 1770-1786 [PMID: 30140036 DOI: 10.1038/s41379-018-0110-y]
- 4 **Alevroudis E**, Spei ME, Chatziioannou SN, Tsoli M, Wallin G, Kaltsas G, Daskalakis K. Clinical Utility of ¹⁸F-FDG PET in Neuroendocrine Tumors Prior to Peptide Receptor Radionuclide Therapy: A Systematic Review and Meta-Analysis. *Cancers (Basel)* 2021; **13** [PMID: 33920195 DOI: 10.3390/cancers13081813]
 - 5 **Shah MH**, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P, Chan J, Das S, Dickson PV, Fanta P, Giordano T, Halfdanarson TR, Halperin D, He J, Heaney A, Heslin MJ, Kandeel F, Kardan A, Khan SA, Kuvshinoff BW, Lieu C, Miller K, Pillarisetty VG, Reidy D, Salgado SA, Shaheen S, Soares HP, Soulen MC, Strosberg JR, Sussman CR, Trikalinos NA, Uboha NA, Vijayvergia N, Wong T, Lynn B, Hochstetler C. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; **19**: 839-868 [PMID: 34340212 DOI: 10.6004/jnccn.2021.0032]
 - 6 **Scoazec JY**, Couvelard A, Monges G, Guyétant S, Bisot-Locard S, Parot X, Lepage C; PRONET Study Group. Professional Practices and Diagnostic Issues in Neuroendocrine Tumour Pathology: Results of a Prospective One-Year Survey among French Pathologists (the PRONET Study). *Neuroendocrinology* 2017; **105**: 67-76 [PMID: 27442514 DOI: 10.1159/000448431]
 - 7 **Yao JC**, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; **26**: 3063-3072 [PMID: 18565894 DOI: 10.1200/JCO.2007.15.4377]
 - 8 **Mollazadegan K**, Welin S, Crona J. Systemic Treatment of Gastroenteropancreatic Neuroendocrine Carcinoma. *Curr Treat Options Oncol* 2021; **22**: 68 [PMID: 34110508 DOI: 10.1007/s11864-021-00866-9]
 - 9 **Sorbye H**, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, Dueland S, Hofslø E, Guren MG, Ohrling K, Birkemeyer E, Thiis-Evensen E, Biagini M, Gronbaek H, Soveri LM, Olsen IH, Federspiel B, Assmus J, Janson ET, Knigge U. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol* 2013; **24**: 152-160 [PMID: 22967994 DOI: 10.1093/annonc/mds276]
 - 10 **Heetfeld M**, Chougnat CN, Olsen IH, Rinke A, Borbath I, Crespo G, Barriuso J, Pavel M, O'Toole D, Walter T; other Knowledge Network members. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 2015; **22**: 657-664 [PMID: 26113608 DOI: 10.1530/ERC-15-0119]
 - 11 **Jeong H**, Shin J, Jeong JH, Kim KP, Hong SM, Kim YI, Ryu JS, Ryoo BY, Yoo C. Capecitabine plus temozolomide in patients with grade 3 unresectable or metastatic gastroenteropancreatic neuroendocrine neoplasms with Ki-67 index <55%: single-arm phase II study. *ESMO Open* 2021; **6**: 100119 [PMID: 33901869 DOI: 10.1016/j.esmoop.2021.100119]
 - 12 **Lamberti G**, Pusceddu S, Ibrahim T, Bongiovanni A, Berardi R, Torniai M, Prinzi N, Manuzzi L, Campana D. First-line fluoropyrimidine and oxaliplatin chemotherapy in gastroentero-pancreatic grade 3 well-differentiated neuroendocrine tumours (NET G3). Proceedings of the Annals of Oncology, 2020. Elsevier: Amsterdam, Netherlands: S776-S776
 - 13 **Carlsen EA**, Fazio N, Granberg D, Grozinsky-Glasberg S, Ahmadzadehfar H, Grana CM, Zandee WT, Cwikla J, Walter MA, Oturai PS, Rinke A, Weaver A, Frilling A, Gritti S, Arveschoug AK, Meirovitz A, Knigge U, Sorbye H. Peptide receptor radionuclide therapy in gastroenteropancreatic NEN G3: a multicenter cohort study. *Endocr Relat Cancer* 2019; **26**: 227-239 [PMID: 30540557 DOI: 10.1530/ERC-18-0424]
 - 14 **Clemente O**, Ottaiano A, Di Lorenzo G, Bracigliano A, Lamia S, Cannella L, Pizzolorusso A, Di Marzo M, Santorsola M, De Chiara A, Fazioli F, Tafuto S. Is immunotherapy in the future of therapeutic management of sarcomas? *J Transl Med* 2021; **19**: 173 [PMID: 33902630 DOI: 10.1186/s12967-021-02829-y]
 - 15 **Patel SP**, Othus M, Chae YK, Giles FJ, Hansel DE, Singh PP, Fontaine A, Shah MH, Kasi A, Baghdadi TA, Matrana M, Gatalica Z, Korn WM, Hayward J, McLeod C, Chen HX, Sharon E, Mayerson E, Ryan CW, Plets M, Blanke CD, Kurzrock R. A Phase II Basket Trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART SWOG 1609) in Patients with Nonpancreatic Neuroendocrine Tumors. *Clin Cancer Res* 2020; **26**: 2290-2296 [PMID: 31969335 DOI: 10.1158/1078-0432.CCR-19-3356]
 - 16 **Bongiovanni A**, Maiorano BA, Azzali I, Liverani C, Bocchini M, Fausti V, Di Menna G, Grassi I, Sansovini M, Riva N, Ibrahim T. Activity and Safety of Immune Checkpoint Inhibitors in Neuroendocrine Neoplasms: A Systematic Review and Meta-Analysis. *Pharmaceuticals (Basel)* 2021; **14** [PMID: 34067837 DOI: 10.3390/ph14050476]
 - 17 **Pellat A**, Cottreau AS, Palmieri LJ, Soyer P, Marchese U, Brezault C, Coriat R. Digestive Well-Differentiated Grade 3 Neuroendocrine Tumors: Current Management and Future Directions. *Cancers (Basel)* 2021; **13** [PMID: 34070035 DOI: 10.3390/cancers13102448]
 - 18 **Botling J**, Lamarca A, Bajic D, Norlén O, Lönnngren V, Kjaer J, Eriksson B, Welin S, Hellman P, Rindi G, Skogseid B, Crona J. High-Grade Progression Confers Poor Survival in Pancreatic Neuroendocrine Tumors. *Neuroendocrinology* 2020; **110**: 891-898 [PMID: 31658459 DOI: 10.1159/000504392]

- 19 **Sorbye H**, Baudin E, Perren A. The Problem of High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms: Well-Differentiated Neuroendocrine Tumors, Neuroendocrine Carcinomas, and Beyond. *Endocrinol Metab Clin North Am* 2018; **47**: 683-698 [PMID: [30098724](#) DOI: [10.1016/j.ecl.2018.05.001](#)]
- 20 **Tang LH**, Untch BR, Reidy DL, O'Reilly E, Dhall D, Jih L, Basturk O, Allen PJ, Klimstra DS. Well-Differentiated Neuroendocrine Tumors with a Morphologically Apparent High-Grade Component: A Pathway Distinct from Poorly Differentiated Neuroendocrine Carcinomas. *Clin Cancer Res* 2016; **22**: 1011-1017 [PMID: [26482044](#) DOI: [10.1158/1078-0432.CCR-15-0548](#)]
- 21 **Mehnert JM**, Bergsland E, O'Neil BH, Santoro A, Schellens JHM, Cohen RB, Doi T, Ott PA, Pishvaian MJ, Puzanov I, Aung KL, Hsu C, Le Tourneau C, Hollebecque A, Élez E, Tamura K, Gould M, Yang P, Stein K, Piha-Paul SA. Pembrolizumab for the treatment of programmed death-ligand 1-positive advanced carcinoid or pancreatic neuroendocrine tumors: Results from the KEYNOTE-028 study. *Cancer* 2020; **126**: 3021-3030 [PMID: [32320048](#) DOI: [10.1002/ncr.32883](#)]
- 22 **Strosberg J**, Mizuno N, Doi T, Grande E, Delord JP, Shapira-Frommer R, Bergsland E, Shah M, Fakih M, Takahashi S, Piha-Paul SA, O'Neil B, Thomas S, Lolkema MP, Chen M, Ibrahim N, Norwood K, Hadoux J. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Neuroendocrine Tumors: Results From the Phase II KEYNOTE-158 Study. *Clin Cancer Res* 2020; **26**: 2124-2130 [PMID: [31980466](#) DOI: [10.1158/1078-0432.CCR-19-3014](#)]
- 23 **Vijayvergia N**, Dasari A, Deng M, Litwin S, Al-Toubah T, Alpaugh RK, Dotan E, Hall MJ, Ross NM, Runyen MM, Denlinger CS, Halperin DM, Cohen SJ, Engstrom PF, Strosberg JR. Pembrolizumab monotherapy in patients with previously treated metastatic high-grade neuroendocrine neoplasms: joint analysis of two prospective, non-randomised trials. *Br J Cancer* 2020; **122**: 1309-1314 [PMID: [32152503](#) DOI: [10.1038/s41416-020-0775-0](#)]
- 24 **Mulvey C**, Raj NP, Chan JA, Aggarwal RR, Cinar P, Hope TA, Kolli K, Zhang L, Calabrese S, Grabowsky JA, Modarresi L, Kelly V, Stonely D, Munster PN, Reidy DL, Fong L, Bergsland EK. Phase II study of pembrolizumab-based therapy in previously treated extrapulmonary poorly differentiated neuroendocrine carcinomas: Results of Part A (pembrolizumab alone). *J Clin Oncol* 2019; **37**: 363 [DOI: [10.1200/JCO.2019.37.4_suppl.363](#)]
- 25 **Yao JC**, Strosberg J, Fazio N, Pavel ME, Bergsland E, Ruzzniewski P, Halperin DM, Li D, Tafuto S, Raj N, Campana D, Hijioka S, Raderer M, Guimbaud R, Gajate P, Pusccheddu S, Reising A, Degtyarev E, Shilkrot M, Eddy S, Singh S. Spartalizumab in metastatic, well/poorly-differentiated neuroendocrine neoplasms. *Endocr Relat Cancer* 2021 [PMID: [33480358](#) DOI: [10.1530/ERC-20-0382](#)]
- 26 **Fottner C**, Apostolidis L, Ferrata M, Krug S, Michl P, Schad A, Roth W, Jaeger D, Galle PR, Weber MM. A phase II, open label, multicenter trial of avelumab in patients with advanced, metastatic high-grade neuroendocrine carcinomas NEC G3 (WHO 2010) progressive after first-line chemotherapy (AVENEC). *J Clin Oncol* 2019; **37**: 4103 [DOI: [10.1200/JCO.2019.37.15_suppl.4103](#)]
- 27 **Kaufman HL**, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, Lebbé C, Linette GP, Milella M, Brownell I, Lewis KD, Lorch JH, Chin K, Mahnke L, von Heydebreck A, Cuillerot JM, Nghiem P. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncol* 2016; **17**: 1374-1385 [PMID: [27592805](#) DOI: [10.1016/S1470-2045\(16\)30364-3](#)]
- 28 Abstracts Presented at the 13th Annual Multidisciplinary Neuroendocrine Tumor Medical Virtual Symposium of the North American Neuroendocrine Tumor Society, October 2-3, 2020. *Pancreas* 2021; **50**: 441-467 [PMID: [33835977](#) DOI: [10.1097/MPA.0000000000001763](#)]
- 29 **Gile JJ**, Liu AJ, McGarrah PW, Eiring RA, Hobday TJ, Starr JS, Sonbol MB, Halfdanarson TR. Efficacy of Checkpoint Inhibitors in Neuroendocrine Neoplasms: Mayo Clinic Experience. *Pancreas* 2021; **50**: 500-505 [PMID: [33939660](#) DOI: [10.1097/MPA.0000000000001794](#)]
- 30 **Lu M**, Zhang P, Zhang Y, Li Z, Gong J, Li J, Li Y, Zhang X, Lu Z, Wang X, Zhou J, Peng Z, Wang W, Feng H, Wu H, Yao S, Shen L. Efficacy, Safety, and Biomarkers of Toripalimab in Patients with Recurrent or Metastatic Neuroendocrine Neoplasms: A Multiple-Center Phase Ib Trial. *Clin Cancer Res* 2020; **26**: 2337-2345 [PMID: [32086343](#) DOI: [10.1158/1078-0432.CCR-19-4000](#)]
- 31 **Cives M**, Pelle' E, Quaresmini D, Rizzo FM, Tucci M, Silvestris F. The Tumor Microenvironment in Neuroendocrine Tumors: Biology and Therapeutic Implications. *Neuroendocrinology* 2019; **109**: 83-99 [PMID: [30699437](#) DOI: [10.1159/000497355](#)]
- 32 **Griffioen AW**, Damen CA, Blijham GH, Groenewegen G. Tumor angiogenesis is accompanied by a decreased inflammatory response of tumor-associated endothelium. *Blood* 1996; **88**: 667-673 [PMID: [8695814](#) DOI: [10.1182/blood.V88.2.667.bloodjournal882667](#)]
- 33 **Manegold C**, Dingemans AC, Gray JE, Nakagawa K, Nicolson M, Peters S, Reck M, Wu YL, Brustugun OT, Crinò L, Felip E, Fennell D, Garrido P, Huber RM, Marabelle A, Moniuszko M, Mornex F, Novello S, Papotti M, Pérol M, Smit EF, Syrigos K, van Meerbeek JP, van Zandwijk N, Yang JC, Zhou C, Vokes E. The Potential of Combined Immunotherapy and Antiangiogenesis for the Synergistic Treatment of Advanced NSCLC. *J Thorac Oncol* 2017; **12**: 194-207 [PMID: [27729297](#) DOI: [10.1016/j.jtho.2016.10.003](#)]
- 34 **Shrimali RK**, Yu Z, Theoret MR, Chinnasamy D, Restifo NP, Rosenberg SA. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. *Cancer Res* 2010; **70**: 6171-6180 [PMID: [20631075](#) DOI: [10.1158/0008-5472.CAN-10-0153](#)]
- 35 **Jimenez C**, Fazeli S, Román-Gonzalez A. Antiangiogenic therapies for pheochromocytoma and

- paranglioma. *Endocr Relat Cancer* 2020; **27**: R239-R254 [PMID: 32369773 DOI: 10.1530/ERC-20-0043]
- 36 **Lin Y**, Xu J, Lan H. Tumor-associated macrophages in tumor metastasis: biological roles and clinical therapeutic applications. *J Hematol Oncol* 2019; **12**: 76 [PMID: 31300030 DOI: 10.1186/s13045-019-0760-3]
- 37 **Xu J**, Shen L, Bai C, Wang W, Li J, Yu X, Li Z, Li E, Yuan X, Chi Y, Yin Y, Lou W, Xu N, Bai Y, Zhang T, Xiu D, Wang X, Yuan Y, Chen J, Qin S, Jia R, Lu M, Cheng Y, Zhou Z, He J, Su W. Surufatinib in advanced pancreatic neuroendocrine tumours (SANET-p): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; **21**: 1489-1499 [PMID: 32966810 DOI: 10.1016/S1470-2045(20)30493-9]
- 38 **Xu J**, Shen L, Zhou Z, Li J, Bai C, Chi Y, Li Z, Xu N, Li E, Liu T, Bai Y, Yuan Y, Li X, Wang X, Chen J, Ying J, Yu X, Qin S, Yuan X, Zhang T, Deng Y, Xiu D, Cheng Y, Tao M, Jia R, Wang W, Fan S, Peng M, Su W. Surufatinib in advanced extrapancreatic neuroendocrine tumours (SANET-ep): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; **21**: 1500-1512 [PMID: 32966811 DOI: 10.1016/S1470-2045(20)30496-4]
- 39 **Cao Y**, Lu M, Sun Y, Gong J, Li J, Lu Z, Zhang X, Li Y, Peng Z, Zhou J, Wang X, Shen L. Surufatinib Plus Toripalimab in Patients with Advanced Solid Tumors: A Single-Arm, Open-Label, Phase I Trial. 2020 Preprint. Available from: Research Square [DOI: 10.21203/rs.3.rs-125321/v1]
- 40 **Shen L**, Yu X, Lu M, Zhang X, Cheng Y, Zhang Y, Li Z, Xu J, Weng D, Wu C, Ma Y, Cheng K, WANG W, Gao H, Li Y, Zhou J, Shi H, Tan P, Su W. Surufatinib in combination with toripalimab in patients with advanced neuroendocrine carcinoma: Results from a multicenter, open-label, single-arm, phase II trial. *J Clin Oncol* 2021; **39**: e16199 [DOI: 10.1200/JCO.2021.39.15_suppl.e16199]
- 41 **Halperin DM**, Liu S, Dasari A, Fogelman DR, Bhosale P, Mahvash A, Dervin S, Estrella J, Cortazar P, Maru DM, Mckenna EF, Wistuba II, Schulze K, Futreal PA, Darbonne WC, Yun C, Hwu P, Yao JC. A phase II trial of atezolizumab and bevacizumab in patients with advanced, progressive neuroendocrine tumors (NETs). *J Clin Oncol* 2020; **38**: 619 [DOI: 10.1200/JCO.2020.38.4_suppl.619]
- 42 **Wright K**. FDA Approves Nivolumab Plus Ipilimumab for the Treatment of Advanced HCC. *Oncology (Williston Park)* 2020; **34** [PMID: 32293694]
- 43 **Campbell MT**, Xie W, Shah AY, Habra MA, Jimenez C, Venkatesan AM, Bublely G, McKay RR, Choueiri TK, McGregor BA, Killbridge KL, Mortazavi A, Bilen MA. Initial results of a phase II study of nivolumab and ipilimumab in metastatic adrenal tumours. *Ann Oncol* 2019; **30** [DOI: 10.1093/annonc/mdz249.082]
- 44 **Wright K**. FDA Approves Nivolumab Plus Ipilimumab for Previously Untreated Unresectable Malignant Pleural Mesothelioma. *Oncology (Williston Park)* 2020; **34**: 502-503 [PMID: 33206991 DOI: 10.46883/ONC.2020.3411.0502]
- 45 **Klein O**, Kee D, Markman B, Michael M, Underhill C, Carlino MS, Jactett L, Lum C, Scott C, Nagrial A, Behren A, So JY, Palmer J, Cebon J. Immunotherapy of Ipilimumab and Nivolumab in Patients with Advanced Neuroendocrine Tumors: A Subgroup Analysis of the CA209-538 Clinical Trial for Rare Cancers. *Clin Cancer Res* 2020; **26**: 4454-4459 [PMID: 32532787 DOI: 10.1158/1078-0432.CCR-20-0621]
- 46 **Patel SP**, Mayerson E, Chae YK, Strosberg J, Wang J, Konda B, Hayward J, McLeod CM, Chen HX, Sharon E, Othus M, Ryan CW, Plets M, Blanke CD, Kurzrock R. A phase II basket trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART) SWOG S1609: High-grade neuroendocrine neoplasm cohort. *Cancer* 2021; **127**: 3194-3201 [PMID: 33882143 DOI: 10.1002/cncr.33591]
- 47 **Capdevila J**, Teule A, López C, García-Carbonero R, Benavent M, Custodio A, Cubillo A, Alonso V, Gordo TA, Carmona-Bayonas A, Crespo G, Blanco-Codesido M, Jimenez-Fonseca P, Viúdez A, La Casta Muñoz A, Sevilla I, Llanos M, Segura A, Hernando-Cubero J, Manzano JL. 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). *Ann Oncol* 2020; **31**: S770-S771 [DOI: 10.1016/j.annonc.2020.08.1370]
- 48 **Chan JA**, Raj NP, Aggarwal RR, Calabrese S, DeMore A, Dhawan MS, Fattah D, Fong L, Grabowsky J, Hope TA, Kolli KP, Munster PN, Perez K, Reidy DL, Fedak SV, Zhang L, Bergsland EK. Phase II study of pembrolizumab-based therapy in previously treated extrapulmonary poorly differentiated neuroendocrine carcinomas: Results of Part B (pembrolizumab + chemotherapy). *J Clin Oncol* 2021; **39**: 4148 [DOI: 10.1200/JCO.2021.39.15_suppl.4148]
- 49 **Owen DH**, Wei L, Goyal A, Zhou Y, Suffren SA, Jacob R, Pilcher C, Otterson GA, Verschraegen CF, Shah MH, Konda B. CLO20-054: A Phase 2 Trial of Nivolumab and Temozolomide in Advanced Neuroendocrine Tumors (NETs): Interim Efficacy Analysis. *JNCCN* 2020; **18**: CLO020-054 [DOI: 10.6004/jnccn.2019.7460]
- 50 **Takahashi D**, Kojima M, Suzuki T, Sugimoto M, Kobayashi S, Takahashi S, Konishi M, Gotohda N, Ikeda M, Nakatsura T, Ochiai A, Nagino M. Profiling the Tumour Immune Microenvironment in Pancreatic Neuroendocrine Neoplasms with Multispectral Imaging Indicates Distinct Subpopulation Characteristics Concordant with WHO 2017 Classification. *Sci Rep* 2018; **8**: 13166 [PMID: 30177687 DOI: 10.1038/s41598-018-31383-9]
- 51 **de Hossion LD**, Takkenkamp TJ, Kats-Ugurlu G, Bouma G, Bulthuis M, de Vries EGE, van Faassen M, Kema IP, Walenkamp AME. Neuroendocrine tumours and their microenvironment. *Cancer Immunol Immunother* 2020; **69**: 1449-1459 [PMID: 32270230 DOI: 10.1007/s00262-020-02556-1]

- 52 **Ali AS**, Langer SW, Federspiel B, Hjortland GO, Grønbaek H, Ladekarl M, Welin S, Weber Vestermark L, Arola J, Osterlund P, Knigge U, Sørbye H, Micke P, Grimelius L, Grönberg M, Tiensuu Janson E. PD-L1 expression in gastroenteropancreatic neuroendocrine neoplasms grade 3. *PLoS One* 2020; **15**: e0243900 [PMID: [33315908](#) DOI: [10.1371/journal.pone.0243900](#)]
- 53 **La Salvia A**, Barroso G, Espinosa Olarte P, Anton Pascual B, Modrego Sanchez A, Riesco-Martinez M, Garcia-Carbonero R. High TMB and MSI-high as independent predictors of survival in NENs. *Proceedings of the J Neuroendocrinol*, 2021. Wiley, Hoboken: NJ, USA: 108
- 54 **Wang S**, Fang Y, Jiang N, Xing S, Li Q, Chen R, Yi X, Zhang Z, Li N. Comprehensive Genomic Profiling of Rare Tumors in China: Routes to Immunotherapy. *Front Immunol* 2021; **12**: 631483 [PMID: [33732253](#) DOI: [10.3389/fimmu.2021.631483](#)]
- 55 **Samstein RM**, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, Barron DA, Zehir A, Jordan EJ, Omuro A, Kaley TJ, Kendall SM, Motzer RJ, Hakimi AA, Voss MH, Russo P, Rosenberg J, Iyer G, Bochner BH, Bajorin DF, Al-Ahmadie HA, Chaft JE, Rudin CM, Riely GJ, Baxi S, Ho AL, Wong RJ, Pfister DG, Wolchok JD, Barker CA, Gutin PH, Brennan CW, Tabar V, Mellinghoff IK, DeAngelis LM, Ariyan CE, Lee N, Tap WD, Gounder MM, D'Angelo SP, Saltz L, Stadler ZK, Scher HI, Baselga J, Razavi P, Klebanoff CA, Yaeger R, Segal NH, Ku GY, DeMatteo RP, Ladanyi M, Rizvi NA, Berger MF, Riaz N, Solit DB, Chan TA, Morris LGT. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat Genet* 2019; **51**: 202-206 [PMID: [30643254](#) DOI: [10.1038/s41588-018-0312-8](#)]
- 56 **Duan X**, Hao S, Zhao M, Mi L, Shi J, Li N, Yin X, Han X, Han G, Wang J. Mismatch repair protein and PD-1/PD-L1 expression in pancreatic neuroendocrine neoplasm. *Proceedings of the J Neuroendocrinol*, 2021. Wiley, Hoboken: NJ, USA: 106
- 57 **Venizelos A**, Elvebakken H, Perren A, Nikolaienko O, Deng W, Lothe IMB, Couvelard A, Hjortland GO, Sundlöv A, Svensson JB, Garresori H, Kersten C, Hofslie E, Detlefsen S, Krogh M, Sorbye H, Knappskog S. The molecular characteristics of high-grade gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 2021 [PMID: [34647903](#) DOI: [10.1530/ERC-21-0152](#)]
- 58 **Rodriguez-Freixinos V**, Chan D, Doherty M, Wasson K, Lscoe N, Raskin W, Hallet J, Myrehaug S, Law C, Thawer A. Avelumab in Unresectable/Metastatic, Progressive, Poorly Differentiated, Grade 3 Neuroendocrine Carcinomas (NECs). *Proceedings of the 17th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease*. 2020 Mar 11-13. *Neuroendocrinology*: 217
- 59 **Uboha NV**, Milhem MM, Kovacs C, Amin A, Magley A, Purkayastha DD, Piha-Paul SA. Phase II study of spartalizumab (PDR001) and LAG525 in advanced solid tumors and hematologic malignancies. *J Clin Oncol* 2019; **37**: 2553 [DOI: [10.1200/JCO.2019.37.15_suppl.2553](#)]
- 60 **Morse M**, Halperin DM, Uronis HE, Hsu DS, Hurwitz H, Bolch E, Warren D, Haley S, John L, Moyer A, Rushing CN, Niedzwiecki D. Phase Ib/II study of pembrolizumab with lanreotide depot for advanced, progressive gastroenteropancreatic neuroendocrine tumors (PLANET). *J Clin Oncol* 2021; **39**: 369 [DOI: [10.1200/JCO.2021.39.3_suppl.369](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

