Review Article

Advances in understanding and management of high-grade pancreatic neuroendocrine neoplasm: a comprehensive review

Dileep Kumar Reddy Regalla[1]^, Ojasvi Deep[2], Ravi Kumar Paluri[2]^

[1]Department of Hospital Medicine, OSF Saint Anthony Medical Center, Rockford, IL, USA; [2]Division of Hematology-Oncology, Department of Internal Medicine, Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC, USA

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Correspondence to: Ravi Kumar Paluri, MD, MPH, FACP. Associate Professor, Division of Hematology-Oncology, Department of Internal Medicine, Atrium Health Wake Forest Baptist Comprehensive Cancer Center, 1 Medical Center Blvd., Winston-Salem, NC 27157, USA. Email: rpaluri@wakehealth.edu.

Abstract: High-grade (HG) pancreatic neuroendocrine neoplasms (PAN-NENs) are aggressive and have a poor prognosis. Yet, our understanding and treatment approaches for these tumors have rapidly evolved in the past decade, despite a lack of prospective and randomized trials. It is essential to differentiate grade 3 (G3) neuroendocrine tumors (NETs) from neuroendocrine carcinomas (NECs) due to their different prognostic and treatment implications. The molecular landscape of HG PAN-NENs is complex, with mutations in key cancer-related genes, extensive genomic rearrangements, and chromosomal instability. Advanced studies have provided insights into the significant genetic heterogeneity of HG PAN-NENs and potential therapeutic targets. Several therapeutic strategies have emerged from molecular characterization studies. These include agents targeting the mammalian target of rapamycin (mTOR) pathway, DNA repair pathways, and epigenetic modifiers. Moreover, high programmed cell death ligand 1 (PD-L1) expression in some tumors indicates potential for immunotherapy. However, many challenges remain, with a deeper understanding of the genetic and epigenetic alterations in these tumors necessary to develop novel therapeutic strategies and improve patient outcomes. Treatment strategies for HG PAN-NENs vary. Looking to the future, many clinical trials are exploring novel therapies or combinations of known therapies to improve outcomes. It is evident that understanding the molecular landscape of PAN-NECs, alongside personalized therapeutic strategies, is crucial to developing effective treatment options and improving patient outcomes. In this discourse, our emphasis will be on the molecular landscape and available treatment strategies for HG PAN-NECs.

Keywords: Pancreatic neuroendocrine tumor grade 3 (PAN-NET G3); neuroendocrine carcinomas (NECs); high-grade neuroendocrine neoplasms (HG NENs); PAN-NENs; PAN neuroendocrine (PNEC)

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^ ORCID: Dileep Kumar Reddy Regalla, 0000-0001-8028-4899; Ravi Kumar Paluri, 0000-0002-2317-7082.

Introduction

Neuroendocrine neoplasms (NENs) are a subset of epithelial tumors with a majority of neuroendocrine (enterochromaffin) cells (1). The terminology of NEN has evolved rapidly in the past two decades. In 2019, the World Health Organization (WHO) revised the previously endorsed European Neuroendocrine Tumor Society (ENETS) grading scheme and classified high-grade (HG) digestive NENs into well-differentiated and poorly differentiated neoplasms (2). Well-differentiated neoplasms [neuroendocrine tumors (NETs)] are subdivided into three grades: grade (G)1, G2, and G3 depending on the mitotic index and Ki-67 index (*Table 1*) (3). Poorly differentiated neoplasms [neuroendocrine carcinoma (NEC)] are by default G3 and subdivided into small cell and large cell types (4). HG pancreatic (PAN)-NENs that include G3 well-differentiated NETs and NEC are aggressive with poor prognosis. Over the past decade, there has been a rapid evolution in our understanding of HG NENs, but we lack innovative treatment strategies. It is important to note that there is still a lack of prospective and randomized trials in this field. In this discussion, we will focus on the management of HG PAN-NENs.

Clinical characteristics

PAN-NET account for <1% to 2% of all PAN tumors and have an incidence of <1 case per 1,00,000 individuals per year (5,6). PAN-NEC presents a complex clinical challenge due to its rare incidence, aggressive nature, and poor prognosis. PAN-NECs account for approximately 20% of NECs arising in the gastrointestinal tract (7). WHO 2019 classification subdivided NECs into small-cell and large-cell carcinomas (8). Histology and immunohistochemistry are used to differentiate NEC from G3 NET. PAN-NECs frequently lose the expression of traditional neuroendocrine markers, such as synaptophysin and chromogranin A. Instead, they may express markers associated with other types of cancers, complicating their diagnosis (9,10). Occasionally, PAN-NECs stain positive for synaptophysin but negative for chromogranin (8). Insulinoma-associated protein 1 (INSM1) is increasingly used to differentiate PAN-NET, from non-NET, and has 100% sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) (11). NEC routinely exhibits Rb loss, *KRAS* mutation, and *TP53* mutation with abnormal P53 staining pattern (12,13).

G3 NET

According to the PRONET study, the proportion of G3 NET among NECs is about 20% (14). PRONET is an epidemiologic prospective study done by French pathologists for 1 year to assess the histopathologic characteristics of newly diagnosed NETs. With the updated WHO 2019 NETs classification, an increasing incidence of G3 NETs was presumed due to widespread awareness among oncologists and pathologists. Nevertheless, it is crucial to differentiate G3 NETs from NECs due to prognostic and treatment implications. G3 NETs routinely stain positive for synaptophysin and chromogranin as well as somatostatin receptor 2A (SSTR2A) (12,15). This staining pattern has prognostic and therapeutic implications which will be discussed below.

Molecular landscape

PAN-NECs of the pancreas often exhibit complex genomic alterations. Mutations in key cancer-related genes, such as *TP53*, *RB1*, *MEN1*, and *DAXX/ATRX*, have been reported in various studies (10,16,17). High levels of chromosomal instability led to extensive genomic rearrangements and copy number variations in PAN ductal (PD)-NECs (18). Recent studies have advanced our understanding of the molecular landscape of HG PAN-NECs, underscoring the significant genetic heterogeneity and revealing potential diagnostic, prognostic, and therapeutic targets. Recent genomic studies have shed light on the genetic alterations underlying PAN-NEC. These alterations include mutations in *TP53* and *RB1*, chromosomal instability, and aberrations in DNA repair genes (18). Comprehensive genomic profiling studies have further characterized these tumors, demonstrating a distinct mutational profile compared to well-differentiated NETs (19). Aberrant DNA methylation and histone modifications are the epigenetic alterations that have been observed in NECs, leading to altered gene expression profiles and contributing to the loss of differentiation (17). PAN-NECs often show activation of specific signaling pathways, such as the mammalian target of rapamycin (mTOR) pathway and Notch signaling, which play crucial roles in tumor growth and progression (10,18). Also, PAN-NECs could be classified into ductal and acinar types based on genomic profiling. *CDKN2A* silencing and alteration of *WNT* signaling are the commonly seen genomic alterations in the acinar type in contrast to the ductal type that involves *KRAS* mutation (9).

Table 1 WHO classification and grading criteria for NENs, 2019 (3)

Type	Differentiation	Ki-67 index (%)	Grade	Mitotic rate (/mm^2)
NET, G1	Well-differentiated	<3	Low	<2
NET, G2	Well-differentiated	3–20	Intermediate	2–20
NET, G3	Well-differentiated	>20	High	>20
NEC, small cell type	Poorly differentiated	>20	High	>20
NEC, large cell type	Poorly differentiated	>20	High	>20
Mixed neuroendocrine/non-NEN	Well- or poorly differentiated	Varies	Varies	Varies

WHO, World Health Organization; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; G, grade; NEC, neuroendocrine carcinoma.

Genomic aberrations in *TP53* and *RB1* genes are frequently observed in extrapulmonary NEN (EP-NEN) (20,21). EP-NENs exhibit somatic alterations in DNA damage repair (DDR) genes, although the prevalence varies depending on the genes evaluated, ranging from 2.5% to 70.6% (22,23). Activation of *MYC* family genes and disruption of epigenetic regulation is a prevalent oncogenic process in EP-NENs. Many samples from various origins show alterations in at least one epigenetic regulator, with genes like *ARID1A*, *KMT2*, and *KMD* family genes being frequently affected (24,25). Dysregulation of the *PI3K/AKT/mTOR* pathway is recurrently observed in EP-NENs from different sites of origin (26). Microsatellite instability-high (MSI-high) status is variable in EP-NENs, with frequencies ranging from 0% to 69.2%. MSI-high is more common in NENs originating from the gastric and colorectal regions, occurring in up to 90% to 97% of cases in these sites (27).

Several potential therapeutic targets have emerged from the molecular characterization of PAN-NECs. Agents targeting *mTOR*, DNA repair pathways, and epigenetic modifiers have been explored in preclinical and clinical studies. Mutations in DNA repair genes suggest a potential role for *PARP* inhibitors, and immunohistochemistry has revealed high programmed cell death ligand 1 (PD-L1) expression in some tumors, suggesting potential for immunotherapy (28). While significant strides have been made in the molecular characterization of PAN-NEC, many challenges remain. A deeper understanding of the genetic and epigenetic alterations in these tumors could enable the development of novel therapeutic strategies and improve patient outcomes.

Treatment for HG PAN-NEN

Surgery

Surgical resection has been well described in G1 and G2 PAN-NETs. Palliative debulking surgery in NECs remains controversial and in a systematic review conclusion on overall survival (OS) could not be drawn (29). A multicenter study among 60 patients with localized HG digestive NEN (72% NEC) showed an OS of 58.5% 2 years after radical surgery among the NEC sub-group (30). Five-year OS was better in the surgical group compared to the non-surgical group in a study (39% *vs.* 10%) among 2,245 patients with localized G3 digestive NEN (31). Radical surgery was associated with better OS compared to no surgery in localized NEC in a propensity analysis (32). Finally, survival analysis showed a trend toward improvement in OS in patients with gastroenteropancreatic (GEP)-NEC treated with local resection (33).

Chemotherapy

Platinum-based therapy

Most digestive NEC studies didn't elucidate whether chemotherapy was adjuvant or neo-adjuvant. Adjuvant chemotherapy after curative resection showed improved outcomes in a cohort study among 1,861 patients with localized digestive NEC. In this study, 519 patients underwent curative resection and 224 patients received postoperative chemotherapy (34). In a similar fashion, chemotherapy showed a better prognosis post-operatively in a retrospective analysis in localized digestive NEC

patients (35). In contrast, postoperative chemotherapy did not improve prognosis in a national database analysis done among 759 patients with localized digestive NEC (36). There is a paucity of prospective trials that have concluded an optimal first-line chemotherapy for PAN-NECs. The NORDIC study is a retrospective analysis of 252 patients with G3 GEP-NEC with the majority (40%) of patients with PAN-NET. Response rates were 15% and 55% in patients with a Ki-67 index less than 55% and a Ki-67 index greater than 55% respectively. Nevertheless, a higher Ki-67 index conferred a poor prognosis. There was no difference in efficacy or progression-free survival (PFS) between cisplatin and carboplatin in the NORDIC study. Interestingly, PAN-NEC had a better prognosis compared to the colorectal NEC in this study (37). Reiterating the above, a European multicenter retrospective analysis among 204 G3 NEN with a majority (32%) primary PAN-NET was retrospectively analyzed. PFS (2.4 *vs.* 5 months, P=0.049) and disease control rate (DCR) (33% *vs.* 68%, P=0.03) were lower in G3 NET compared to NEC. However, the median OS was significantly longer in NET G3. Of note, the median Ki-67 index was 30 in G3 NET *vs.* 70 in NEC (38). Both oral and intravenous carboplatin were noted to have similar efficacy and safety in a retrospective study of 11 patients with NEC, and the overall response rate (ORR) was around 40% (*Figure 1*) (39). Another retrospective analysis included 45 patients with G3 PAN-NEN. Response rates were 10% in well-differentiated G3 PAN-NETs *vs.* 37% in PAN-NEC in patients treated with platinum agents. In contrast, response rates were 50% in well-differentiated G3 PAN-NET as well as in NEC in patients treated with alkylating agents (40). Considering the above studies, platinum-etoposide may not be a first-line option for G3 PAN-NET, especially in the setting of a low Ki-67 index.

Based on the findings above, few studies have evaluated FOLFOX [5-fluorouracil (5-FU), leucovorin, oxaliplatin] in G3 NET. A retrospective analysis at Mayo Clinic included 30 patients with G3 NET (70% PAN-NET) who were treated with platinum-etoposide (n=8) and FOLFOX (n=7). Median PFS was 2.94 months in the platinum group compared to 13.04 months FOLFOX group even though both had a similar radiographic response rate (41). Additionally, a multicenter retrospective analysis among G3 NET showed an ORR of 35.1% for the platinum-etoposide combination (n=37) compared to 56.4% for FOLFOX (n=39) (42). Additionally, another retrospective analysis among G3 NET patients showed a better OS and PFS with an alkylating-based regimen compared to platinum-etoposide (43).

TOPIC-NEC randomized 170 digestive NEC patients into irinotecan and cisplatin regimen *vs.* etoposide and cisplatin regimen. OS was similar in both groups however G3 and G4 adverse effects were more common in the etoposide group (44).

Second-line chemotherapy

A randomized trial compared FOLFIRI plus bevacizumab (n=65) with FOLFIRI alone (n=68) in patients with GEP-NEC. There was no difference in OS between the two groups (45). Another randomized study compared nanoliposomal-irinotecan (nal-IRI) plus 5-FU with docetaxel in GEP-NEC patients. Only nal-IRI/5-FU reached the threshold efficacy to be tested in the phase-III trial. There is an unmet need to establish a second-line chemotherapy regimen in treating patients with NEC (46).

Temozolomide-based therapy

A recent retrospective analysis evaluated 468 patients with HG NEN (71% with PAN primary) who received capecitabine/temozolomide (CAPTEM). G3 NETs had a median PFS of 27 months and median OS of 36 months when compared to NECs where PFS was 7 months and median OS was 14 months. These results were statistically significant. Interestingly, patients with a PAN primary had a significantly better ORR compared to non-PAN primary (47). Another retrospective analysis done at Mayo Clinic evaluated CAPTEM in G3 NET patients (71% PAN primary) with an ORR of 35% and median PFS of 9.4 months (41). A retrospective analysis showed an ORR of 41% in G3 NEN patients treated with CAPTEM (48). Finally, another retrospective study showed a 70% objective radiographic response rate and, median PFS of 18 months among 30 patients with metastatic, well/moderate differentiated PAN-NET (49). This response rate is better than the streptozocin-based regimen. (50) Based on the studies above CAPTEM is an acceptable regimen in G3 PAN-NETs.

Tyrosine kinase inhibitor

A retrospective analysis among 15 patients with well/moderate differentiated PAN-NET with four patients treated with everolimus showed sustained PFS for at least

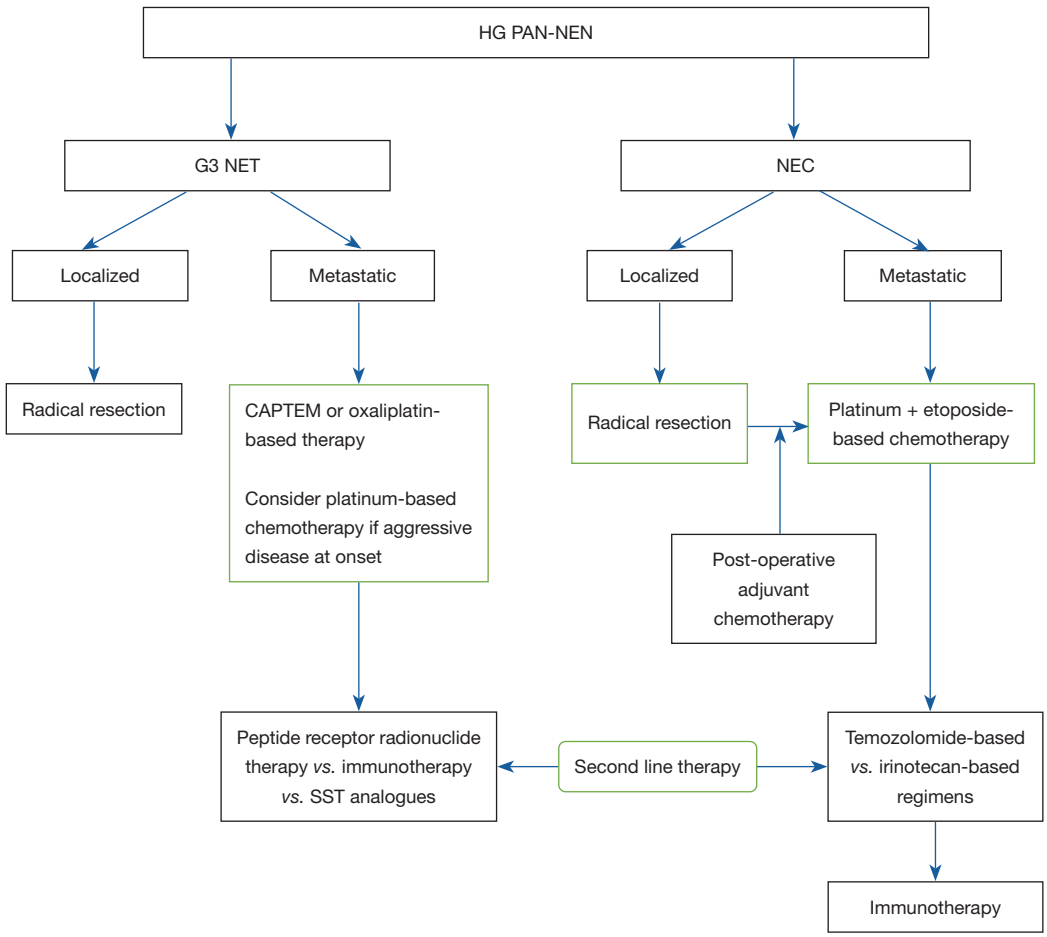

Figure 1 An outline for the treatment of HG PAN-NEN (39). Surgery should be considered for localized G3 NET and NEC. CAPTEM or oxaliplatin-based regimen such as FOLFOX is the well-described first-line chemotherapy option for G3 NET. Peptide receptor radionuclide therapy, immunotherapy, and SST analogues are the second-line options. For metastatic NEC, platinum + etoposide is the well-studied first-line chemotherapy including in post-operative adjuvant setting. Second-line treatment options include CAPTEM, nal-IRI + 5-FU with docetaxel. Immunotherapy could be considered as a third-line option. HG, high-grade; PAN-NEN, pancreatic neuroendocrine neoplasm; G, grade; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; CAPTEM, capecitabine/temozolomide; SST, somatostatin; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; nal-IRI, nanoliposomal-irinotecan; 5-FU, 5-fluorouracil.

12 months (51). It was noted that Ki-67 index was less than 55% in these patients. As already known, everolimus is approved by the Food and Drug Administration (FDA) for the treatment of G1 and G2 PAN-NET (52). However, further studies are necessary to validate the use of everolimus in G3 PAN-NET.

Immunotherapy

Data on PD-L1 inhibitors and programmed death-1 (PD-1) inhibitors in G3 PAN-NEN is very limited. A retrospective analysis at the Mayo Clinic studied 57 patients with NETs treated with checkpoint inhibitors. Patients with NEC had an ORR of 13% compared to 0% in G3 NEN (53). Similarly, a retrospective study of 34 patients with HG NEN (majority with PAN primary) showed an ORR of 14.7% and a DCR of 41.2%. Of note, this response is seen only in NEC patients (54). A phase II study enrolled 34 patients with HG NEN (around 30% PAN primary) and patients were treated with pembrolizumab, objective response rate was 3.4% with a DCR (24.1%) (55). More recently, AVENEC phase 2 study interim analysis reported

a DCR of 32% after 8 weeks of treatment with avelumab (anti-PD-L1 antibody) in patients with HG NEN (56). In addition, a prospective trial showed an ORR of 26% in HG NEN patients who were treated with ipilimumab plus nivolumab. A total of 19 patients were included in the HG NEN cohort among which 11% were PAN primary (57).

Somatostatin (SST) analogues

SST analogues help in both symptoms related to hormone secretion and cytostatic control (58). In a study of 35 patients with progressive NET, SST analogues achieved stable response in 57% of patients (59). Among these 35 patients, 9 patients did not receive prior chemotherapy, 18 patients had one to two lines of chemotherapy and 8 patients received three to four lines of chemotherapy before initiating SST analogues. Evaluation of 41 patients with G3 NET (58% primary PAN) showed a PFS of 7.9 months for SST analogues (60). In this study, a total of 19 patients received SST analogues among which it was first-line treatment in 16 patients and second-line in the remaining. The use of SST analogues in G3 NET could be considered, however, it would be beneficial to obtain molecular imaging to derive the expression of SSTR. In contrast, NECs do not typically express SSTR, the use of SST analogues is questionable, and no data is available.

Sunitinib

Clinical experience with sunitinib in G3 NET and NEC is limited to a few studies. A Japanese retrospective study of 10 patients with G3 PAN-NET who were treated with sunitinib had an ORR of 60%, and 30% of the patients had a stable disease (61). Another study showed that high A-PKT expression decreases response to sunitinib in HG GEP-NEN (62).

Peptide receptor radionuclide therapy (PRRT)

A retrospective cohort study with 149 patients (89 patients with PAN primary) has aimed to demonstrate the efficacy of PRRT in G3 GEP-NET. The median PFS was 14 months, and the median OS was 29 months (63). Lutetium-177 (^{177}Lu)-DOTATATE is FDA-approved for SSTR-positive NET. A survival analysis among 69 patients with HG NEN (predominant PAN-NEN) showed that PRRT is effective in patients with Ki-67 index less than 55% who failed chemotherapy (64). Another retrospective analysis among 28 patients with G3 NEN treated with PRRT has shown better median PFS among patients with a Ki-67 index less than 55% compared to the patients with Ki-67 index greater than 55% (65). A study of 19 patients with well-differentiated HG NET (74% PAN primary) found a DCR of 72% (66). A similar study on HG GEP-NET with (^{177}Lu)-DOTATATE found a DCR of 87% in patients with Ki-67 less than 35% (67). PRRT for PAN-NEC like SST analogues is questionable due to sparse expression of SSTR in NEC. Based on the findings above, PRRT is a viable option for G3 PAN-NET and probably for selected cases of PAN-NEC with a low Ki-67 index. It is important to note that PRRT for G3 NET is not approved in many countries and trial enrollment is recommended.

Below we propose a treatment flowchart based on the currently available evidence for HG PAN-NEN.

Future directions

Many clinical trials are currently examining novel therapies or combinations of known therapies to improve the outcomes of PAN-NEC (*Table 2*). Most of the trials are not specific to PAN-NEC but they are included in combinations with other cancers such as small-cell cancers.

Conclusions

PAN-NECs are infrequent, yet they exhibit a swift growth pattern and lead to unfavorable prognoses. A thorough review by a skilled pathologist, evaluating factors such as histology, immunohistochemistry, proliferation index, and mutation analysis, is essential. Distinguishing G3 NETs from NECs using these insights plays a pivotal role in shaping personalized treatment approaches. Although the 2019 WHO classification has enhanced the precision of diagnoses, there is a significant deficit of innovative treatment strategies. Particularly for NECs, the potential effectiveness of treatments like SST analogues, everolimus, and PRRT is uncertain. In addition, there are no proven second-line chemotherapy regimens for PAN-NECs. The role and potential benefits of immune checkpoint inhibitors in both PAN-NETs and PAN-NECs still require further investigation. It is clear that there is an urgent need for more prospective randomized trials. Besides, an improved understanding of the molecular characteristics of these tumors could inform the development of novel diagnostic

Table 2 Ongoing trials for NEC

NCT number	Phase	Population	Arms	Line of therapy	Primary objective	Secondary objective
NCT03647163	I/II	NEC, NSCLC, ST	VSV-IFNβ-NIS + pembrolizumab	≥2	ORR, safety	OS, PFS, DOR, DCR, AE
NCT05420636	2	SCLC and HG NEC	Iadademstat [selective inhibitor of LSD1 (KDM1A)] + paclitaxel	≥2	ORR	SAE, PFS
NCT04802174	I/II	SCLC and HG NEC	Berzosertib + lurbinectedin	≥2	MTD, RR (PR + CR)	Safety, PK, and PD
NCT04429087	1	DLL3 + SCLC, NEC	BI764532 (DLL3/CD3 bispecific T-cell engager)	≥2	MTD, DLT	ORR, PK
NCT05619744	1	SCLC and HG NEC	RO7616789 (anti-DLL3 bispecific antibody) + tocilizumab	≥2	AE and SAE, DOR, ORR, DCR, PFS, OS	PK, anti-drug antibody prevalence
NCT04538378	2	SCLC, NSCLC, NEC	Olaparib + durvalumab	≥2	ORR	PFS, OS, safety
NCT04042714	2	Extra pulmonary	TAS-102	≥2	ORR	OS and PFS
NCT05262556	Pilot	Extra pulmonary	TQ formula plus nivolumab and ipilimumab	≥2	Safety	TTP
NCT05058651	2/3	Extra pulmonary	Az + platinum + etoposide-maintenance Az *vs.* observation	1	OS	PFS, DOR, ORR, DCR
NCT01824875	2	PNEC	Cap + TEM *vs.* TEM	≥2	PFS	ORR, OS
NCT02595424	2	PNEC + GI tract	Cap + TEM *vs.* carboplatin + cisplatin + etoposude	1	PFS	RR, OS, AE

Line of therapy: ≥2, refractory; 1, treatment naïve. NEC, neuroendocrine carcinoma; NCT, national clinical trial; NSCLC, non-small cell lung cancer; ST, solid tumor; VSV-IFNβ-NIS, intravenous oncolytic vesicular stomatitis virus expressing interferon-beta and the sodium iodide symporter; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; DOR, duration of response; DCR, disease control rate; AE, adverse event; SCLC, small cell lung cancer; HG, high-grade; LSD1, lysine-specific demethylase 1; KDM1A, lysine (K)-specific demethylase 1A; SAE, serious AE; MTD, maximum tolerated dose; RR, response rate; PR, partial response; CR, complete response; PK, pharmacokinetics; PD, pharmacodynamics; DLL3, delta-like ligand 3; CD3, cluster of differentiation 3; DLT, dose limiting toxicity; TAS-102, triluridine/tipiracil; TQ, thymoquinone; TTP, time to tumor progression; Az, atezolizumab; PNEC, pancreatic neuroendocrine; Cap, capecitabine; TEM, temozolomide; GI, gastrointestinal.

and therapeutic strategies.

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Footnote

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