IN THE NAME OF GOD

CHEMOTHERAPY IN NEUROENDOCRINE TUMORS

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PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

2019 WHO Classification and Grading Criteria for Neuroendocrine Neoplasms of the Gastrointestinal Tract and Hepatopancreatobiliary Organs

Terminology	Differentiation	Grade	Mitotic rate[a] (mitoses/2 mm²)	Ki-67 index[a] (percent)
NET, G1	Well-differentiated	Low	<2	<3
NET, G2	Well-differentiated	Intermediate	2 to 20	3 to 20
NET, G3	Well-differentiated	High	>20	>20
Neuroendocrine carcinoma (NEC), small cell type (SCNEC)	Poorly differentiated	High[b]	>20	>20
NEC, large cell type (LCNEC)	Poorly differentiated	High[b]	>20	>20
Mixed neuroendocrine-non- neuroendocrine neoplasm	Well or poorly differentiated[c]	Variable[c]	Variable[c]	Variable[c]

[a] Mitotic rates are to be expressed as the number of mitoses/2 mm² (equaling 10 high-power fields at 40× magnification and an ocular field diameter of 0.5 mm) as determined by counting in 50 fields of 0.2 mm² (ie, in a total area of 10 mm²); the Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labeling (hot spots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher grade category.

[b] Poorly differentiated NECs are not formally graded but are considered high grade by definition.

[c] In most mixed neuroendocrine-non-neuroendocrine neoplasms (MINENs or MiNENs), both the neuroendocrine and non-neuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indexes in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well differentiated; when feasible, each component should therefore be graded separately.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

2015 WHO Criteria for the Diagnosis of Pulmonary NET

Tumor type	Criteria
Typical carcinoid	Carcinoid morphology and <2 mitoses/2 mm² (10 high-power fields), lacking necrosis and ≥0.5 cm
Atypical carcinoid	Carcinoid morphology with 2 to 10 mitoses/2 mm² (10 high-power fields) or necrosis (often punctuate)
Large cell neuroendocrine carcinoma	Neuroendocrine morphology (organoid nesting, palisading, rosettes, trabeculae); High mitotic rate ≥11/2 mm² (10 HPFs), median of 70/2 mm²; Necrosis (often large zones); Cytologic features of a NSCLC: large cell size, low nuclear to cytoplasmic ratio, vesicular or fine chromatin, and/or frequent nucleoli; some tumors have fine nuclear chromatin and lack nucleoli but qualify as non-small cell lung cancer because of large cell size and abundant cytoplasm; and Positive immunohistochemical staining for one or more neuroendocrine markers (other than neuron-specific enolase) and/ or neuroendocrine granules by electron microscopy
Small cell neuroendocrine carcinoma	Small size (generally less than the diameter of three resting lymphocytes); Scant cytoplasm; Nuclei: finely granular nuclear chromatin, absent or faint nucleoli; High mitotic rate: ≥11 mitoses/2 mm² (10 high-power fields), median of 80/2 mm² (10 high-power fields); and Frequent necrosis, often in large zones

Reprinted from Travis WD, Colby TV, Corrin B, et al. (1999) WHO Histological Classification of Tumours. Histological Typing of Lung and Pleural Tumours. 3rd ed. Berlin: Springer.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TABLE 1. WHO Classification of NETs of the Lung and Thymus, and GI Tract

		Lung and Thymic NETs		GI NETs	
Differentiation	**Grade**	**Nomenclature**	**Proliferation Rate**	**Nomenclature**	**Proliferation Rate**
Well-differentiated	Low	Typical carcinoid	< 2 mitoses/2 mm^2 and no necrosis	NET, G1	< 2 mitoses/2 mm^2 and Ki-67 $< 3\%$
	Intermediate	Atypical carcinoid	2-10 mitoses/2 mm^2 or necrosis	NET, G2	2-20 mitoses/2 mm^2 and Ki-67 3%-20%
	High	NA	NA	NET, G3	> 20 mitoses/2 mm^2 and Ki-67 $> 20\%$

NOTE. Data adapted.[3,6]

Abbreviations: NA, not applicable; NET, neuroendocrine tumor.

TABLE 2. Key Patient and Tumor Characteristics That Affect Treatment

Hormone Status	Functional	Nonfunctional
Extent and burden of disease	Localized	Metastatic or unresectable
	Liver-dominant	Widely metastatic
	Low-volume	High-volume
Grade	Low-grade	High-grade
Pace of growth	Stable	Progressive
Primary site	Pancreatic	Nonpancreatic
SSTR status	Positive	Negative

Abbreviation: SSTR, somatostatin receptor.

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INTRODUCTION

- The role for chemotherapy in the treatment of NETs is much more nuanced and relevant for select tumor subsets. One reason the role for chemotherapy in NETs is less defined is that these tumors are often slowly proliferating; chemotherapy tends to be most effective against rapidly proliferating malignant cells [10]. Furthermore, the chemotherapy regimens that seem to demonstrate antitumor activity in NETs are different from the chemotherapy regimens (e.g., platinum etoposide doublet and platinum topoisomerase 1 inhibitor doublet) utilized for NECs

. CURRENT EVIDENCE FOR CHEMOTHERAPY IN THE SYSTEMIC SETTING

- **Alkylating Agents**
- **. Streptozocin-Based Regimens**

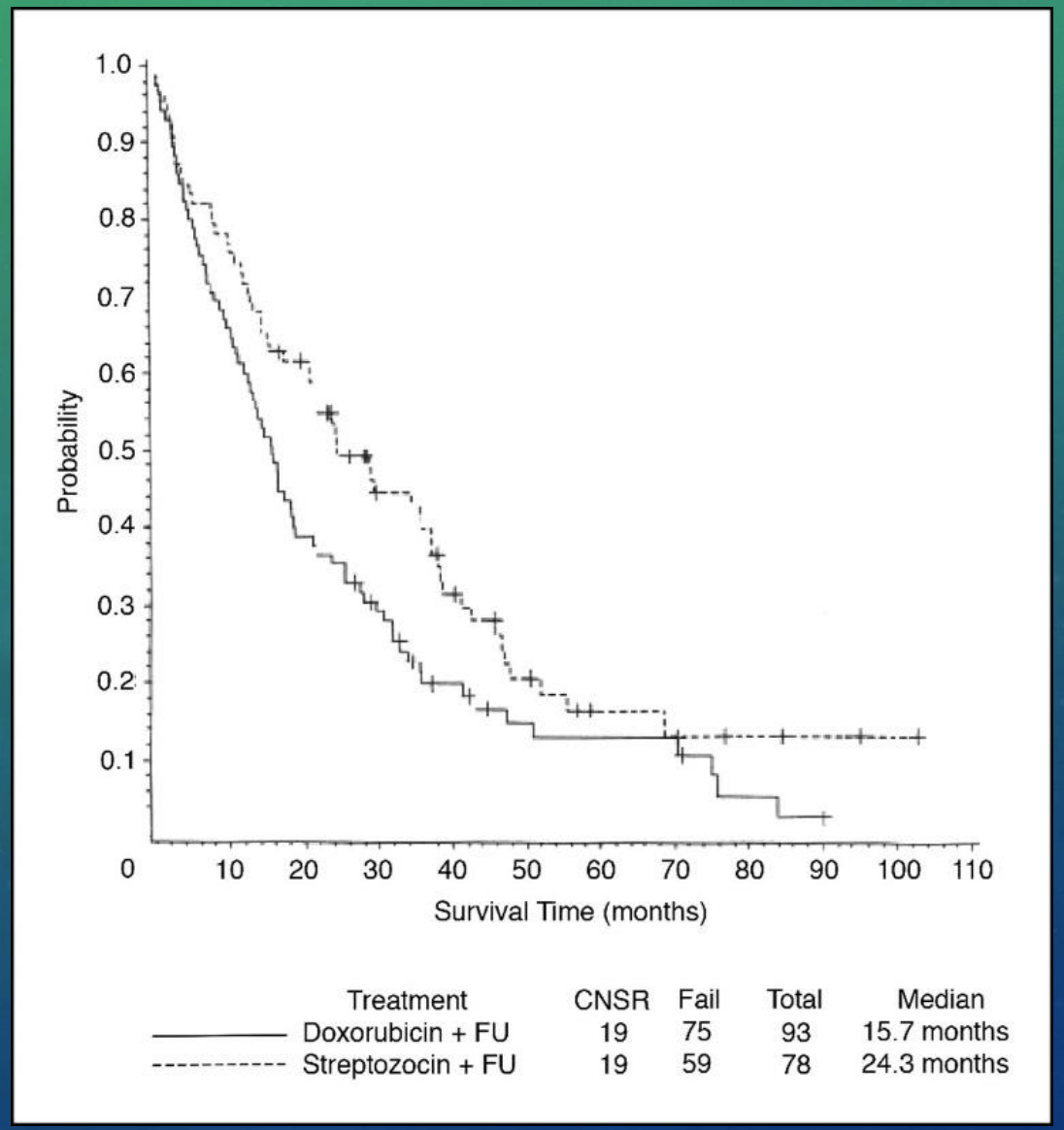
PANCREATIC NETS

- Streptozocin is an antibiotic derived from the Gram-positive bacterium Streptomyces, which demonstrated toxicity against pancreatic cells in animal models

- Combination therapy with streptozocin plus fluorouracil became the treatment standard for patients with advanced pancreatic NETs after demonstrating superior antitumor activity compared to streptozocin monotherapy

- More than a decade later, streptozocin plus doxorubicin was compared against streptozocin plus fluorouracil

- . The ORR was superior with streptozocin plus doxorubicin compared to streptozocin plus fluorouracil (69% vs. 45%, p = 0.05) and chlorozotocin (69% vs. 30%, p = 0.002). The median OS in patients treated with streptozocin plus doxorubicin was significantly longer than patients treated with streptozocin plus fluorouracil or chlorozotocin (2.2 years vs. 1.4 years vs. 1.5 years, p-value not provided).



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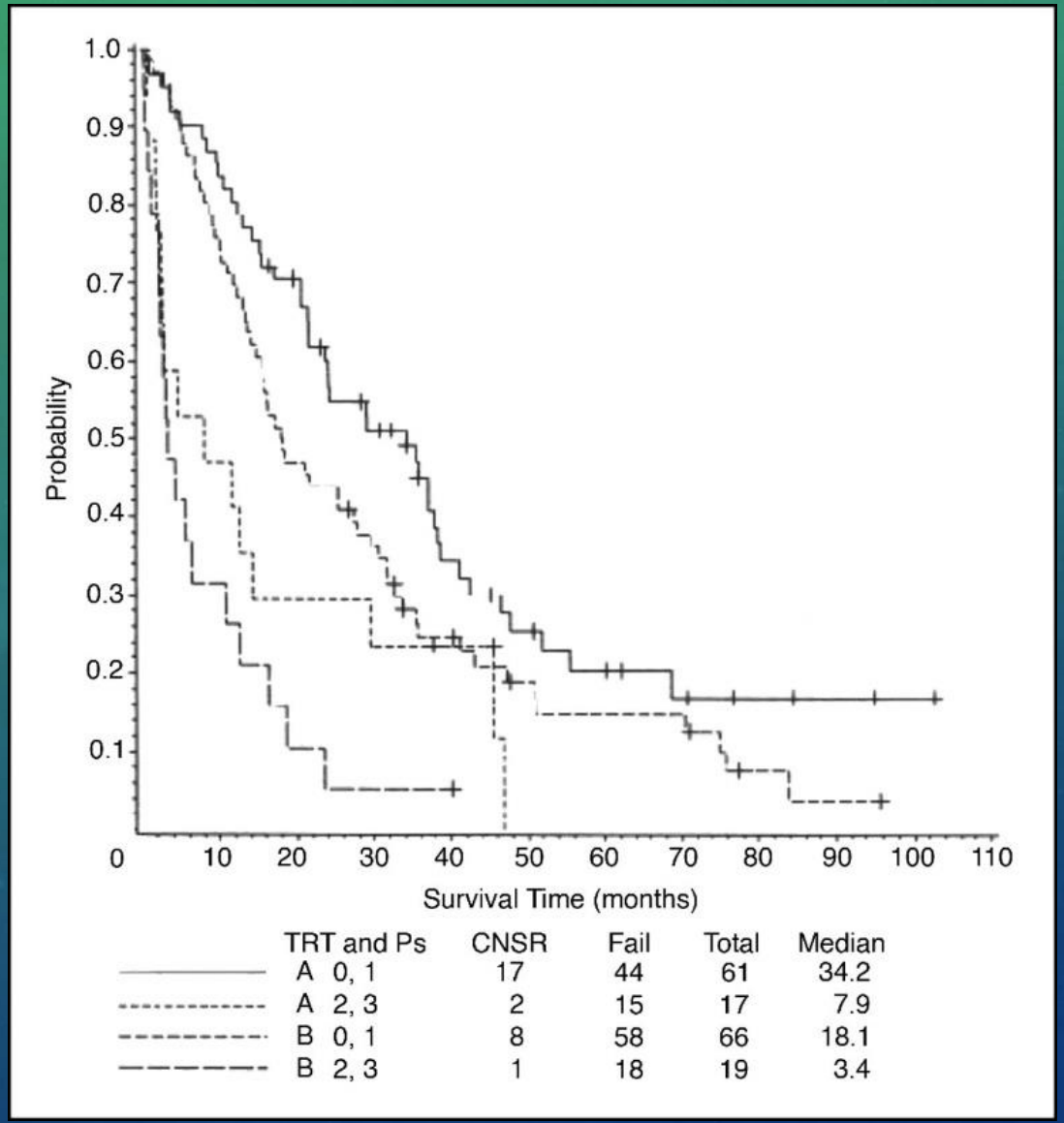

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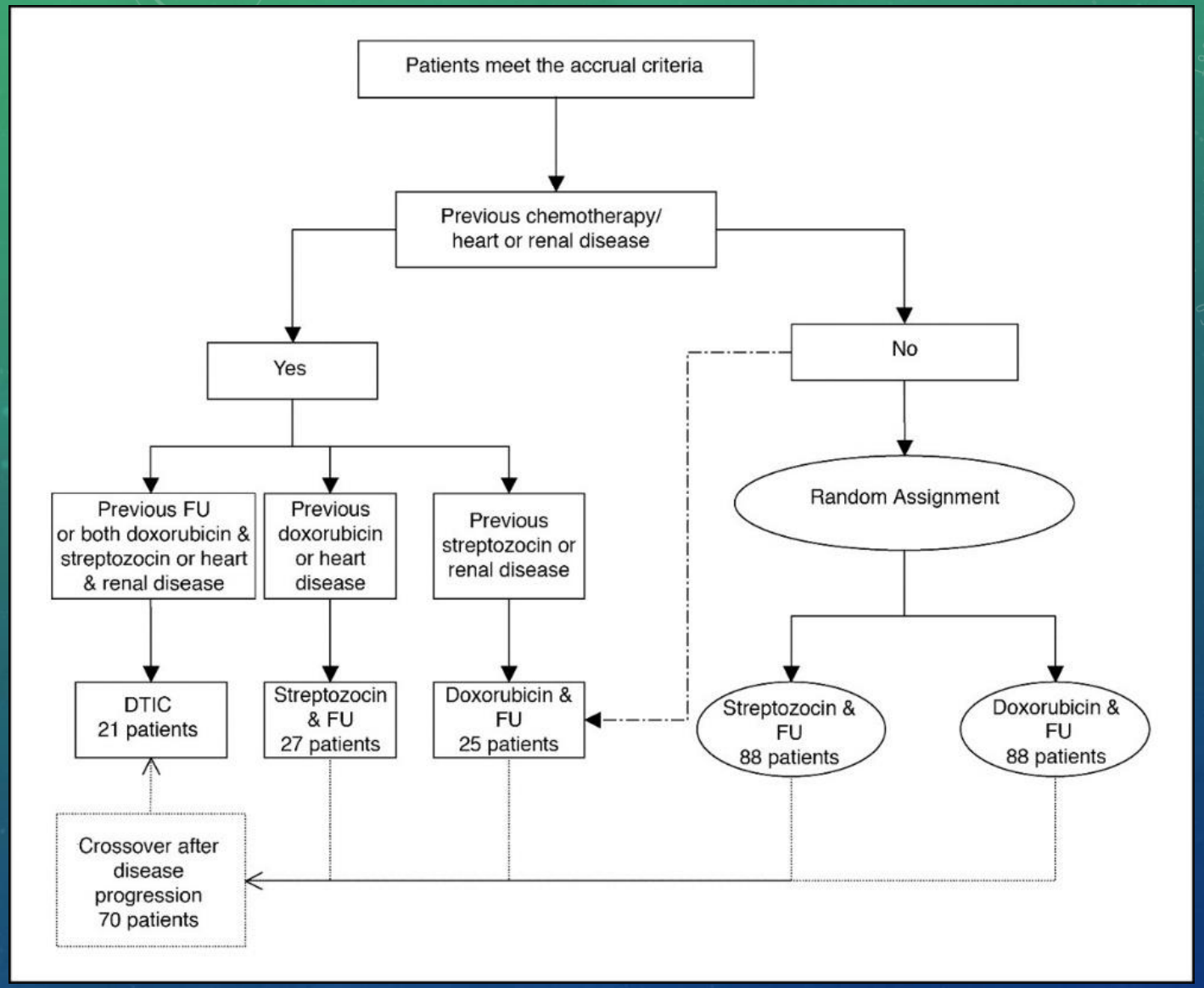
Patients meet the accrual criteria
Previous chemotherapy/ heart or renal disease
Yes
No
Previous FU or both doxorubicin & streptozocin or heart & renal disease
Previous doxorubicin or heart disease
Previous streptozocin or renal disease
Random Assignment
DTIC 21 patients
Streptozocin & FU 27 patients
Doxorubicin & FU 25 patients
Streptozocin & FU 88 patients
Doxorubicin & FU 88 patients
Crossover after disease progression 70 patients

EXTRA-PANCREATIC NETS

- Streptozocin-based regimens have also been tested in patients with extra-pancreatic NETs, which were (and, at times, still are) referred to as carcinoid tumors. A summary of several studies with the agent in patients with extra-pancreatic NETs is presented in Table 1. Relative to the results of studies presented in patients with pancreatic NETs, patients with extra-pancreatic NETs treated with streptozocin-based regimens demonstrated lower ORR and shorter survival times.

Table 1. A summary of prospective studies with streptozocin in patients with extra-pancreatic NETs.

Study	Phase	Regimen	N	Key Findings *
Moertel et al. [18]	NS	STZ + 5-FU	42	ORR 33%
		Cyclo + 5-FU	47	ORR 33%
Engstrom et al. [19]	II/III	STZ + 5-FU	80	ORR 22%, OS 16 m
		DOX	81	ORR 21%, OS 12 m
Bukowski et al. [20]	II	STZ + DOX + 5-FU + cyclo	56	ORR 31%
		STZ + 5-FU + cyclo	9	ORR 22%, OS 10.8 m
Sun et al. [21]	II/III	STZ + 5-FU	27	ORR 16%, OS 24.3 m
		DOX + 5-FU	25	ORR 15.9%, OS 15.7 m
Dahan et al. [22]	III	STZ + 5-FU	64 **	PFS 5.5 m, OS 30.4 m
		Interferon α		PFS 14.1 m, OS 44 m

* All times to event endpoints are reported as median values unless otherwise stated. ORR was not uniformly evaluated by RECIST criteria in these studies. ** A total of 6 patients in this trial possessed pancreatic NETs. None of the PFS and OS differences between the arms were statistically significant. Abbreviations: STZ, streptozocin; 5-FU, fluorouracil; cyclo, cyclophosphamide; DOX, doxorubicin; ORR, overall response rate; m, months; OS, overall survival; PFS, progression-free survival; NS, not specified; +, plus.

1-DACARBAZINE-BASED

REGIMENS PANCREATIC NETS

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DACARBAZINE-BASED REGIMENS PANCREATIC NETS

- Dacarbazine is a prodrug that shares the same active metabolite (5-(3-methyltriazen1-yl) with temozolomide [27]. Given the oral administration and better tolerability of temozolomide, this agent has replaced dacarbazine as a treatment option for patients with NETs. Although the efficacy of dacarbazine vs. temozolomide-based regimens has not been compared in the context of a trial, the two regimens were compared in a retrospective study [28]. A total of 247 patients (82.3% possessed pancreatic NETs, 78.9% with grade 1/2 NETs) were treated with either dacarbazine plus fluorouracil or capecitabine plus temozolomide.

- There was no difference in the Cancers ،ORR (38.3% vs. 39.2%, p = 0.59) or median PFS (p = 0.86)

- , it does suggest that dacarbazine-based combination regimens may have similar activity to temozolomide-based regimens, particularly in patients with pancreatic NETs.

EXTRA-PANCREATIC NETS

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- n a subsequent phase II study, dacarbazine (400 mg/m2 IV D1 and D2) was combined with fluorouracil (1 g/m2 IV D1 and D2) and leucovorin (200 mg/m2 IV D1 and D2) in 21-day cycles [30]. Of the 18 patients, nine possessed nonpancreatic NETs; only one patient experienced a partial response. The efficacy of the treatment was deemed to be insufficient in patients with nonpancreatic NETs

2-TEMOZOLOMIDE-BASED REGIMENS

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TEMOZOLOMIDE-BASED REGIMENS

- **Temozolomide is an oral alkylating agent with improved blood–brain barrier penetration compared to other agents of its class**

- **The combination of capecitabine plus temozolomide is perhaps the temozolomide combination with the strongest preclinical rationale. Capecitabine, along with other fluoropyrimidines, is thought to deplete MGMT, the enzyme responsible for repairing the DNA damage created by temozolomide.**

- The largest retrospective experience to date in patients with well-differentiated NETs treated with capecitabine plus temozolomide was recently published [36]. From a total of 462 patients treated with capecitabine plus temozolomide between 2008 and 2019, 79% possessed well-differentiated NETs. Patients with pancreatic NETs comprised the majority (71.4%) of the included patients in the analysis. The ORR was significantly longer in patients with pancreatic NETs compared to those with extra-pancreatic NETs (51.5% vs. 31.8%, $p < 0.001$). The median PFS (23 months vs. 10 months, $p < 0.001$) and OS (62 vs. 28 months, $p < 0.001$) were significantly longer in patients with pancreatic NETs compared to those with extra-pancreatic NETs.

- Several studies suggested that the maximal time to response occurs within 4–6 months of starting therapy

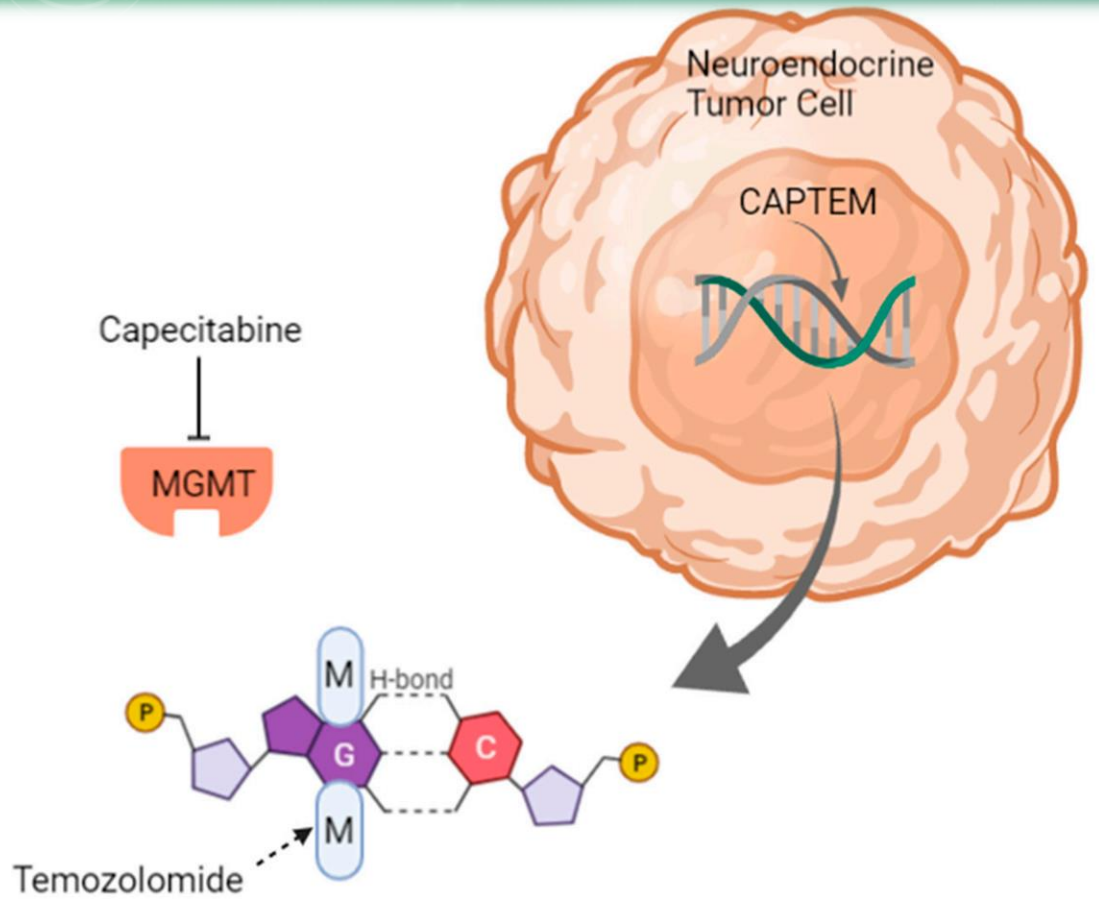

Figure 1. A depiction of the mechanism of action of capecitabine plus temozolomide in a neuroendocrine tumor. Temozolomide adds a methyl group to the O^6 position of guanine, resulting in mismatched bases and cell death. The MGMT enzyme typically transfers methyl groups from the O^6 position of guanine to its cysteine residue; however, this is inhibited by capecitabine. The figure was created in Biorender. Abbreviations: M, methyl group; CAPTEM, capecitabine plus temozolomide; G, guanine; C, cytosine.

EXTRA-PANCREATIC NETS

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EXTRA-PANCREATIC NETS

FROM THE COLLECTION OF STUDIES PRESENTED AND OTHERS PUBLISHED IN THE EXISTING LITERATURE [46], IT APPEARS THAT CAPECITABINE PLUS TEMOZOLOMIDE APPEARS TO ELICIT GREATER TUMOR CYTOREDUCTION AND MORE PROLONGED TUMOR SUPPRESSION IN PANCREATIC NETS COMPARED TO NONPANCREATIC NETS. THERE ARE NO STUDIES WITH THE REGIMEN INDICATING AN APPRECIABLE OBJECTIVE RESPONSE RATE IN MIDGUT NETS.

Table 2. A summary of retrospective studies in patients with extra-pancreatic NETs treated with capecitabine plus temozolomide.

Study	N	PTO of Patients Included	Tumor Grades Included	Median CAPTEM Exposure	Key Findings *
Thomas et al. [40]	69	Mixed	G1,G2 and G3	9.5 cycles	9% ORR, 71% DCR, PFS 11 m, OS 38 m
Crespo et al. [41]	19	Mixed	G1 and G2	8 cycles	36.8% ORR, 94.7% DCR, PFS 15.3 m, OS 41.6 m
Chatzellis et al. [42]	49	Mixed	G1,G2 and G3	12.1 cycles	16.3% ORR, 53% DCR, PFS of GI NETs 6.4 m, OS of GI NETs 13.4 m, PFS of lung/thymic NETs NR, OS of lung/thymic NETs NR
Al-Toubah et al. [36]	132	Mixed	G1, G2 and G3	8 cycles	31.8% ORR, PFS 10 m, OS 28 m
Al-Toubah et al. [43]	20	Lung Only	70% TC, 25% AC, 5% NOS	7.5 months	30% ORR, 85% DCR, PFS 14, OS 68 m
Papaxoinis et al. [44]	33	Lung Only	61% AC, 30% TC, 9% NOS	6 cycles	18.2% ORR, 75.8% DCR, PFS 9 m, OS 30.4 months
Chauhan et al. [45]	12	Unknown Primary	G1,G2 and G3	6 cycles	PFS of G2 NETs 10.8 m, PFS of G3 NETs 7 m

* All times to event endpoints are reported as median values unless otherwise stated. Abbreviations: PTO, primary tumor origin; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; CAPTEM, capecitabine plus temozolomide; TC, typical carcinoid; AC, atypical carcinoid; m, months; G, grade; NR, not reached.

OUTCOMES BASED UPON MGMT STATUS

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OUTCOMES BASED UPON MGMT STATUS

- The MGMT enzyme is responsible for repairing the DNA damage from temozolomide (and other alkylating agents) primarily by removing the methyl group from the O6 position, which restores the DNA of affected cells into a normal conformation [47]. Based upon this mechanistic rationale, it has been hypothesized that patients with NETs with MGMT deficiency should be more sensitive to alkylating agent-based therapy compared to patients with NETs with intact MGMT

- Patients with MGMT-deficient tumors demonstrated a significantly improved ORR compared to patients with tumors with intact MGMT expression (80% vs. 0%, $p = 0.001$). Patients with MGMT-deficient tumors also demonstrated improved median PFS (19.2 months vs. 9.3 months) and median OS (NR vs. 19.1 months) compared to patients with tumors with intact MGMT expression, though these differences were not statistically significant.

At this juncture, the pending correlative analyses from the prospective randomized phase II ECOG 2211 study may best reveal the true association between the tumor MGMT expression status and response to temozolomide.

3-PLATINUM AGENTS

OXALIPLATIN BASED-REGIMENS

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3-PLATINUM AGENTS

OXALIPLATIN BASED-REGIMENS

Oxaliplatin, rather than cisplatin or carboplatin, is the platinum agent that has demonstrated meaningful activity in patients with well-differentiated NETs. The oxaliplatin combination regimen that has been most tested in patients with NETs is fluorouracil plus oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (CAPOX). The DNA-damaging mechanism of action of platinum agents is described in Figure 2.

The largest retrospective experience of patients with well-differentiated NETs treated with FOLFOX reported to date included 88 patients with pancreatic NETs [60]. The ORR in these patients was 31%, the median PFS was 9 months, and the median OS was 30 months. Among the patients with pancreatic NETs, those with insulinomas demonstrated the longest median PFS (22 months).

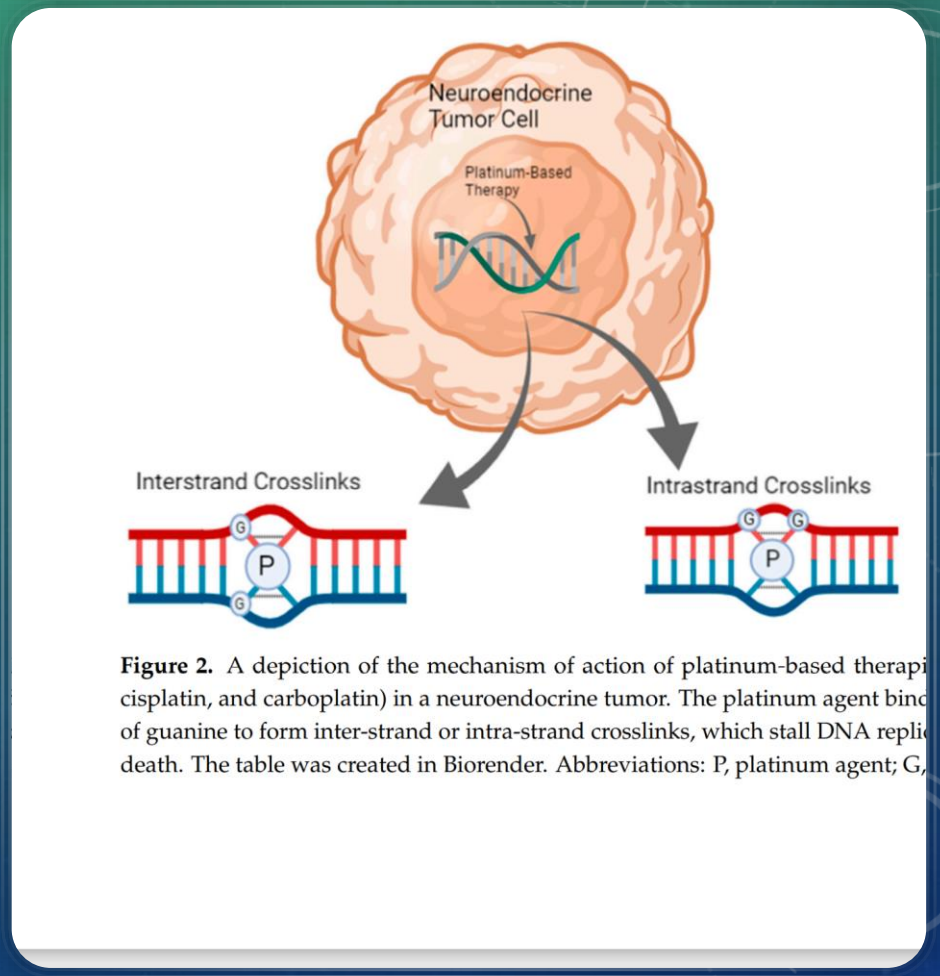

Figure 2. A depiction of the mechanism of action of platinum-based therapi cisplatin, and carboplatin) in a neuroendocrine tumor. The platinum agent binc of guanine to form inter-strand or intra-strand crosslinks, which stall DNA repli death. The table was created in Biorender. Abbreviations: P, platinum agent; G,

EXTRA-PANCREATIC NETS

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EXTRA-PANCREATIC NETS

- In the aforementioned retrospective experience, 37, 13, 7, and 4 patients with small intestinal, unknown primary, gastric, and rectal NETs, respectively, were treated with FOLFOX [60]. The ORR in the patients with small intestinal, unknown primary, gastric, and rectal NETs was 13, 38, 14, and 25%, respectively. The median PFS in the patients with small intestinal, unknown primary, gastric, and rectal NETs was 9 months, 6 months, 14 months, and 4 months, respectively. The median OS in the patients with small intestinal, unknown primary, gastric, and rectal NETs was 28 months, 15 months, 31 months, and 25 months, respectively

- Oxaliplatin-based regimens appear to elicit less tumor cytoreduction in nonpancreatic NETs compared to pancreatic NETs. The duration of the antitumor response, however, appears to be more similar between the tumor types than seen with alkylating agentbased regimens

CHEMOTHERAPY IN GRADE 3 NETS

CISPLATIN OR CARBOPLATIN-BASED REGIMENS

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CHEMOTHERAPY IN GRADE 3 NETS

CISPLATIN OR CARBOPLATIN-BASED REGIMENS

- Grade 3 well-differentiated NETs are a relatively new pathologic entity that only recently were defined as a separate tumor category [62,63]. The majority of grade 3 NETs arise in the pancreas, stomach, or colorectum [64]. Given the heterogeneous behavior of these tumors, a significant degree of uncertainty exists about the optimal chemotherapy regimens for this tumor type.

- An ongoing randomized phase II study is comparing platinum etoposide doublet chemotherapy vs. capecitabine plus temozolomide in patients with grade 3 NENs (including NETs and non-small cell NECs) (NCT02595424). This trial may answer whether platinum-based chemotherapy regimens are most active in patients with NECs or may play a role in the treatment of patients with NETs as well.

. ALKYLATING AGENT-BASED REGIMENS

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. ALKYLATING AGENT-BASED REGIMENS

- Another retrospective study explored the activity of capecitabine plus temozolomide in patients with grade 3 NENs [69]. Of the 32 included patients, 20 possessed gastroenteropancreatic NETs (Ki-67 index range 20–54%), while 12 possessed gastroenteropancreatic NECs (median Ki-67 index ≥ 55%). The predominant primary tumor locations for the patients were the pancreas (40.6%), colorectum (18.7%), and stomach (15.6%). The majority (75%) of patients received the therapy in the second-line and beyond setting. The median PFS in the NET group was significantly higher than in the NEC group (15.3 months vs. 3.3 months, HR 0.18, $p < 0.001$). The median OS in the NET group was also significantly higher in the NET group than in the NEC group (22 months vs. 4.6 months, HR 0.25, $p = 0.0178$). The ORR and DCR in the patients with NETs treated with the regimen was 50% and 70%, respectively. The ORR and DCR in the patients with NECS treated with the regimen was 8.3% and 33%, respectively

OXALIPLATIN-BASED REGIMENS

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OXALIPLATIN-BASED REGIMENS

- **Though this study suggests that the optimal use of FOLFOX may be in the second-line setting for post-temozolomide-based therapy, prospective studies need to be conducted to determine the optimal chemotherapy sequencing.**

. CURRENT EVIDENCE FOR CHEMOTHERAPY IN THE ADJUVANT OR NEOADJUVANT SETTING

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. CURRENT EVIDENCE FOR CHEMOTHERAPY IN THE ADJUVANT OR NEOADJUVANT SETTING

- Other retrospective analyses suggest that neoadjuvant chemotherapy may play a role in patients with metastatic pancreatic NETs. The first of these was a single center analysis that assessed the outcomes in 67 patients with liver-limited pancreatic NETs who underwent R0/R1 resections

- A total of 27 patients received neoadjuvant fluorouracil, doxorubicin, and streptozocin (fluorouracil 400 mg/m2 IV D1-D5, streptozocin 400 mg/mg IV D1-D5, and doxorubicin 40 mg/mg2 IV D1 every 28 days). The median number of neoadjuvant chemotherapy cycles administered was four. Among the patients who received neoadjuvant therapy, the ORR was 63%. Further, 18.5% of the patients initially felt to be unresectable were able to undergo surgical resection. While the patients treated with neoadjuvant therapy had a higher proportion of poor prognostic factors (bulkier disease and synchronous disease), the survival outcomes were the same as the outcomes in the patients treated with surgery alone

. COMBINATORIAL APPROACHES WITH CHEMOTHERAPY

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Table 3. Prospective trials combining chemotherapy with other systemic therapies in patients with NETs.

Study	Phase	N	Regimen	Key Findings *
Pavlakis et al. [79]	II	75	CAPTEM + ^{177}Lu-dotatate (Pancreatic NETs)	12 m-PFS 76%, ORR 68%
			CAPTEM (Pancreatic NETs)	12 m-PFS 67%, ORR 33%
			CAPTEM + ^{177}Lu-dotatate (Midgut NETs)	15 m-PFS 90%, ORR 31%
			^{177}Lu-dotatate (Midgut NETs)	15 m-PFS 92%, ORR 15%
Claringbold et al. [80]	II	33	Capecitabine + ^{177}Lu-dotatate	12 m-PFS 91%, 24 m-PFS 88%
Bhave et al. [81]	I/II	28	Temozolomide + Pazopanib (Pancreatic NETs)	ORR 25%, DCR 70%, PFS 12.1 m and OS 36.2 m
Chan et al. [82]	I/II	43	Temozolomide + Everolimus	ORR 40%, DCR 93%, PFS 15.4 m and OS NR
Owen et al. [83]	II	12	Temozolomide + Nivolumab	ORR 25%, DCR 92%

* All times to event endpoints are reported as median values unless otherwise stated. Abbreviations: PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DCR, disease control rate; m, months; +, plus.

CHEMOTHERAPY PLUS IMMUNOTHERAPY

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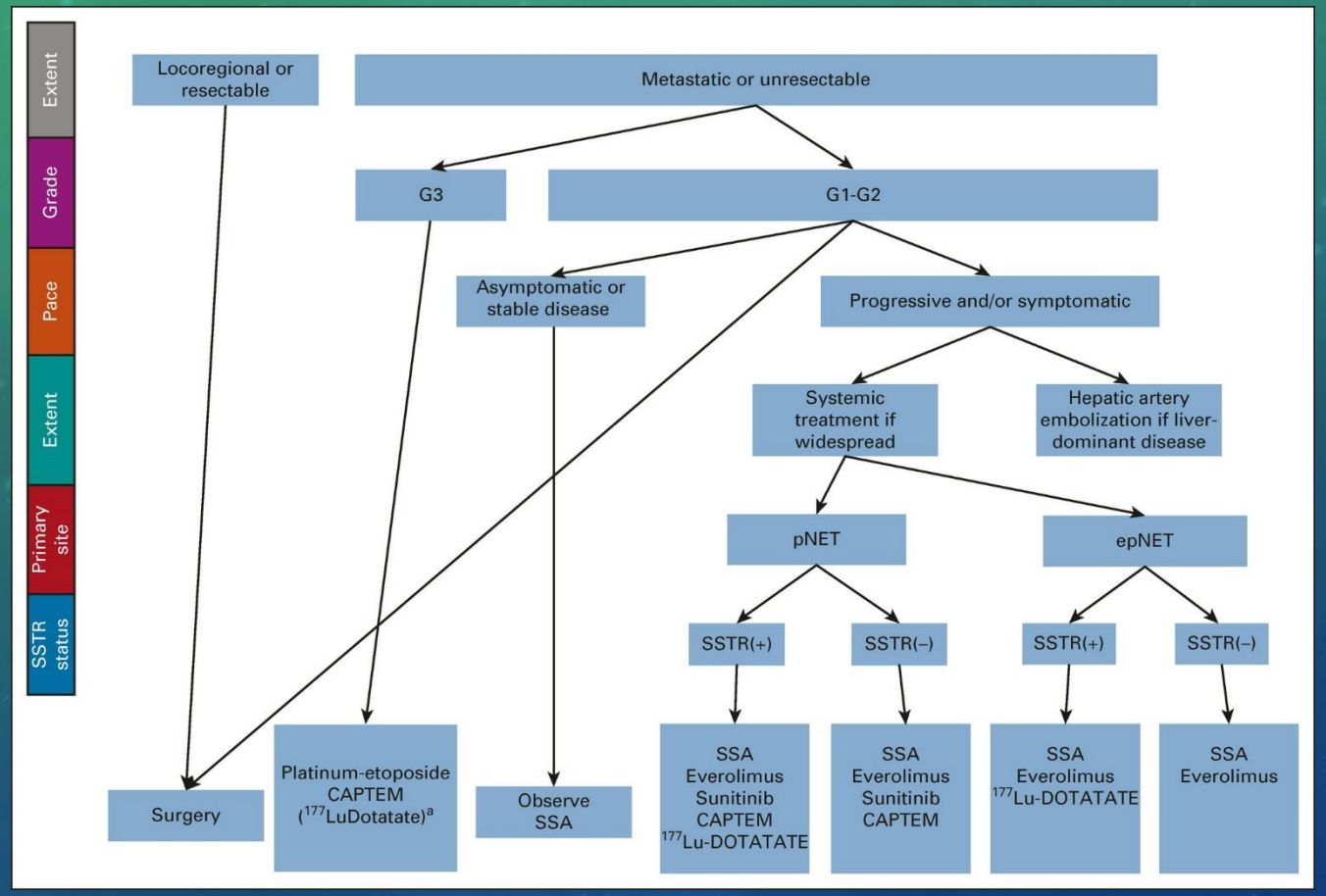
CHEMOTHERAPY PLUS IMMUNOTHERAPY

- The patients in the trial were treated with nivolumab 480 mg IV D1 and temozolomide 150 mg/m2 PO D1-D5 every 28 days. Of the 12 patients in the welldifferentiated NET cohort, the ORR and DCR were 25 and 92%, respectively. The three patients who achieved a partial response all possessed NETs with Ki-67 indexes ≥15%; two patients possessed grade 3 NETs. The study is ongoing, and the final results may inform the future development plan for the combination.

CONCLUSIONS

CONCLUSIONS

- The role of chemotherapy in patients with well-differentiated NETs remains an area of active clinical investigation.
- Patients with pancreatic NETs and grade 3 NETs appear to be the most chemosensitive; however, patients with ≥grade 2 extra-pancreatic NETs may also derive benefits from the treatment modality.
- In patients with pancreatic NETs, the optimal sequencing of chemotherapy in relation to other available therapies is still an area of ongoing investigation.
- The SEQTOR trial, for example, is exploring whether alkylating agent-based therapy should come before or after everolimus.
- A soon-to-be-recruiting clinical trial will explore whether capecitabine plus temozolomide should be offered before or after PRRT.
- Among the extra-pancreatic primary sites, lung NETs appear to be particularly sensitive to capecitabine plus temozolomide, whereas evidence supporting chemotherapy in midgut NETs is almost absent. Thus far, chemotherapy has demonstrated clinically meaningful antitumor activity in patients with advanced (metastatic or unresectable) disease; its role in adjuvant or neoadjuvant settings is as-of-yet undefined.
- Temozolomideand oxaliplatin-based regimens are the most commonly utilized chemotherapies; however, combinations of these regimens with PRRT and targeted therapy are being explored to increase the number of cytoreductive options that may be available for patients with NETs.



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