NCCN Clinical Practice Guidelines in Oncology
(NCCN Guidelines®)

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Neuroendocrine and Adrenal Tumors

Overall management of Neuroendocrine and Adrenal Tumors is described in the full NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Neuroendocrine and Adrenal Tumors. Visit NCCN.org to view the complete library of NCCN Guidelines®.

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Locoregional Advanced and/or Distant Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2)

- **Systemic therapy may not be appropriate for every patient with locoregional advanced and/or distant metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, locoregional therapy, cytoreductive surgery, or systemic therapy, which may be appropriate considerations.**
- **Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.**
- **There is no known role for systemic treatment in the adjuvant setting for NETs.**
- **Doses and schedules are subject to appropriate modifications depending on the circumstances.**
- **For management of hormone-related symptoms for GI tumors, see NET-9. For management of carcinoid syndrome, see NET-14.**

Neuroendocrine Tumors of the Gastrointestinal Tract (Well-Differentiated Grade 1/2)[a]

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Locoregional Advanced Disease and/or Distant Metastases	• Cabozantinib (category 1 if prior treatment with everolimus or lutetium Lu 177 dotatate)[1] • Everolimus (category 1 for nonfunctional tumors)[b,c,2,3] • PRRT with lutetium Lu 177 dotatate (if SSTR-positive and progression on octreotide LAR/lanreotide) (category 1 for progressive mid-gut tumors) (NE-J) • Octreotide LAR[d-g,4,5] or lanreotide[d-g,6,7]	• None	• If progression on standard SSA doses, above-label dose octreotide LAR[h] or lanreotide[h] (if SSTR-positive) • Consider RT ± concurrent fluoropyrimidine-based chemotherapy for locally advanced unresectable disease (excluding small bowel mesenteric) (NE-I) • Consider (listed in alphabetical order): ▸ Cytotoxic chemotherapy, if no other options feasible (all category 3): Anticancer agents such as 5-fluorouracil (5-FU), capecitabine, dacarbazine, oxaliplatin, and temozolomide can be used in patients with progressive disease. (See Discussion for details.)

[a] If clinically significant disease progression, treatment with octreotide LAR or lanreotide should be discontinued for non-functional tumors and continued in patients with functional tumors; these regimens may be used in combination with any of the subsequent options. For details on the administration of octreotide LAR or lanreotide with lutetium Lu 177 dotatate, see NE-J.
[b] Effectiveness of everolimus in the treatment of patients with carcinoid syndrome has not been established.
[c] Phase III study done in nonfunctional tumors.
[d] Treatment with octreotide LAR or lanreotide will likely be of greatest benefit in patients with SSTR-positive tumors.
[e] For symptom and/or tumor control, octreotide LAR 20–30 mg IM or lanreotide 120 mg SC every 4 weeks. Higher doses have been shown to be safe. For breakthrough symptoms, octreotide 100–250 mcg SC TID can be considered.
[f] The PROMID trial showed an antitumor effect of octreotide LAR in advanced NETs of the midgut.[5] The CLARINET trial showed an antitumor effect of lanreotide in advanced, well-differentiated metastatic grade 1 and grade 2 GEP NETs.[6]
[g] If injection site-related complications occur, consider switching to another SSA.
[h] After clinical, symptomatic, or radiographic progression on standard SSA doses, for symptom and/or tumor control, above-label dosing octreotide LAR (up to 60 mg once a month) or lanreotide (up to 120 mg every 14 days) may be useful in select cases.

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Distant Metastatic Neuroendocrine Tumors of Lung and Thymus

- **Systemic therapy may not be appropriate for every patient with distant metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, locoregional therapy, cytoreductive surgery, or systemic therapy, which may be appropriate considerations.**
- **Currently, there are no data to support a specific sequence of regional versus systemic therapy and no data to guide sequencing of the following systemic therapy options.**
- **There is no known role for systemic treatment in the adjuvant setting for NETs.**
- **Doses and schedules are subject to appropriate modifications depending on the circumstances.**
- **For management of carcinoid syndrome, see NET-14.**

Lung/Thymus Neuroendocrine Tumors[a]

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Distant Metastases (clinically significant tumor burden and low grade [typical carcinoid] or evidence of disease progression or intermediate grade [atypical carcinoid] or symptomatic)	• Cabozantinib (category 1 if prior treatment with everolimus)[1] • Everolimus[b,c,2,3] (category 1 for nonfunctional lung NETs) • Octreotide LAR[e,g,5] or lanreotide[e,g,6,8] (if SSTR-positive and/or hormonal symptoms)	• None	• Carboplatin + etoposide[i,9,10] • Cisplatin + etoposide[i,9-11] • PRRT with lutetium Lu 177 dotatate (if SSTR-positive and progression on octreotide LAR or lanreotide) (NE-J) • Temozolomide[12,13] ± capecitabine[i,14,15] • If progression on standard SSA doses, above-label dose octreotide LAR[h] or lanreotide[h] (if SSTR-positive and/or hormonal symptoms) (category 2B)

[a] If clinically significant disease progression, treatment with octreotide LAR or lanreotide should be discontinued for non-functional tumors and continued in patients with functional tumors; these regimens may be used in combination with any of the subsequent options. For details on the administration of octreotide LAR or lanreotide with lutetium Lu 177 dotatate, see NE-J.
[b] Effectiveness of everolimus in the treatment of patients with carcinoid syndrome has not been established.
[c] Phase III study done in nonfunctional tumors.
[e] For symptom and/or tumor control, octreotide LAR 20–30 mg IM or lanreotide 120 mg SC every 4 weeks. Higher doses have been shown to be safe. For breakthrough symptoms, octreotide 100–250 mcg SC TID can be considered.
[g] If injection site-related complications occur, consider switching to another SSA.
[h] After clinical, symptomatic, or radiographic progression on standard SSA doses, for symptom and/or tumor control, above-label dosing octreotide LAR (up to 60 mg once a month) or lanreotide (up to 120 mg every 14 days) may be useful in select cases.
[i] Carboplatin + etoposide, cisplatin + etoposide, or temozolomide ± capecitabine can be considered for intermediate-grade/atypical tumors with Ki-67 proliferative index and mitotic index in the higher end of the defined spectrum.

References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY

Locoregional Advanced and/or Distant Metastatic Pancreatic Neuroendocrine Tumors (Well-Differentiated Grade 1/2)

- **Systemic therapy may not be appropriate for every patient with locoregional advanced and/or distant metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, locoregional therapy, cytoreductive surgery, or systemic therapy.**
- **Currently, there are no data to support a specific sequence of regional versus systemic therapy and no data to guide sequencing of the following systemic therapy options.**
- **There is no known role for systemic treatment in the adjuvant setting for PanNETs.**
- **Doses and schedules are subject to appropriate modifications depending on the circumstances.**
- **For management of hormone-related symptoms and complications, see PanNET-1 through PanNET-10.**

Pancreatic Neuroendocrine Tumors (Well-Differentiated Grade 1/2)[a]

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Locoregional Advanced Disease and/or Distant Metastases	• Cabozantinib (category 1 if prior treatment with everolimus, lutetium Lu 177 dotatate, or sunitinib)[1,16] • Everolimus (category 1 for progressive disease) 10 mg by mouth, daily • Sunitinib[17] (category 1 for progressive disease) 37.5 mg by mouth, daily • Octreotide LAR[e,f,g,j] or lanreotide[e,f,g,j,7] (if SSTR-positive) • PRRT with lutetium Lu 177 dotatate (if SSTR-positive and progression on octreotide LAR or lanreotide)[18] (NE-J) • Temozolomide + capecitabine[19] (preferred when tumor response is needed for symptoms or cytoreduction)	• Cytotoxic chemotherapy options considered in patients with bulky, symptomatic, and/or progressive disease include: ◊ FOLFOX[20] ◊ CAPEOX[21]	• If progression on standard SSA doses, above-label dose octreotide LAR[h,j] or lanreotide[h,j] (if SSTR-positive) • Octreotide LAR[e,g] or lanreotide[e,g] (if SSTR-negative)[22] • Consider belzutifan in the setting of germline *VHL* alteration in patients with progressive PanNETs[k,l,23] • Consider RT ± concurrent fluoropyrimidine-based chemotherapy for locally advanced unresectable disease (excluding small bowel mesenteric) (NE-I)

Footnotes on NE-H 4 of 11
References

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Well-Differentiated, Grade 3 Neuroendocrine Tumors

Well-Differentiated, Grade 3 Neuroendocrine Tumors[24,25]

Locally Advanced/Metastatic Disease with Favorable Biology (Unresectable with Clinically Significant Tumor Burden or Evidence of Disease Progression)	Locoregional Disease (Resectable) with Unfavorable Biology	Locally Advanced/Metastatic Disease with Unfavorable Biology
• Clinical trial (preferred) • Cabozantinib[1] • Chemotherapy (temozolomide ± capecitabine,[m,26] FOLFOX, CAPEOX, cisplatin/etoposide, or carboplatin/etoposide) • Everolimus • Octreotide LAR[e,g] or lanreotide[e,g] (if SSTR-positive and/or hormonal symptoms) (if progression on standard SSA doses, above-label dose octreotide LAR[h] or lanreotide[h] [category 2B]) • Pembrolizumab[n] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • PRRT with lutetium Lu 177 dotatate[o] (if SSTR-positive) (NE-J) • Sunitinib (pancreas only) • Consider RT (NE-I) ± concurrent fluoropyrimidine-based chemotherapy for locally advanced unresectable disease	• Clinical trial (preferred) • Neoadjuvant chemotherapy on a case-by-case basis (eg, Ki-67 ≥55%) ▸ Cisplatin/etoposide or carboplatin/etoposide ▸ Oxaliplatin-based therapy (FOLFOX, CAPEOX) ▸ Temozolomide ± capecitabine[m,26]	• Clinical trial (preferred) • Cisplatin/etoposide or carboplatin/etoposide • Irinotecan-based therapy (eg, FOLFIRI, cisplatin + irinotecan, or FOLFIRINOX) • Oxaliplatin-based therapy (ie, FOLFOX or CAPEOX) • Pembrolizumab[n] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Temozolomide ± capecitabine[m,26] • Nivolumab + ipilimumab[p,27,28] (category 2B) • Consider RT (NE-I) ± concurrent fluoropyrimidine-based chemotherapy for locally advanced unresectable disease

[e] For symptom and/or tumor control, octreotide LAR 20–30 mg IM or lanreotide 120 mg SC every 4 weeks. Higher doses have been shown to be safe. For breakthrough symptoms, octreotide 100–250 mcg SC TID can be considered.
[g] If injection site-related complications occur, consider switching to another SSA.
[h] After clinical, symptomatic, or radiographic progression on standard SSA doses, for symptom and/or tumor control, above-label dosing octreotide LAR (up to 60 mg once a month) or lanreotide (up to 120 mg every 14 days) may be useful in select cases.
[m] Temozolomide ± capecitabine may have more activity in tumors arising in the pancreas compared to GI NETs.
[n] Pembrolizumab can be considered for patients with MSI-H, dMMR, or advanced TMB-H tumors (as determined by an FDA-approved test) that have progressed following prior treatment and have no satisfactory alternative treatment options.
[o] Consider trial of SSA before PRRT. Preliminary data suggest reduced efficacy if high Ki-67 and/or FDG-PET avid.
[p] Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

References

Note: All recommendations are category 2A unless otherwise indicated.

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Please see the accompanying Full Prescribing Information for CABOMETYX® (cabozantinib).

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Indications and Important Safety Information Provided by Exelixis

INDICATIONS

CABOMETYX® (cabozantinib) is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET).

CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extrapancreatic neuroendocrine tumors (epNET).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: CABOMETYX can cause severe and fatal hemorrhages. The incidence of Grade 3-5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3-4 hemorrhage and before surgery. Do not administer to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, and gastrointestinal (GI) perforations, including fatal cases, each occurred in 1% of CABOMETYX patients. Monitor for signs and symptoms, and discontinue CABOMETYX in patients with Grade 4 fistulas or GI perforation.

Thrombotic Events: CABOMETYX can cause arterial or venous thromboembolic event. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events have occurred. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. In CABINET (n=195), hypertension occurred in 65% (26% Grade 3) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with antihypertensive therapy or for hypertensive crisis.

Diarrhea: CABOMETYX can cause diarrhea and it occurred in 62% (10% Grade 3) of treated patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1; resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): CABOMETYX can cause PPE and it occurred in 45% of treated patients (13% Grade 3). Withhold CABOMETYX until PPE resolves or decreases to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria; resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): CABOMETYX can cause ONJ and it occurred in <1% of treated patients. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution; resume at a reduced dose.

Impaired Wound Healing: CABOMETYX can cause impaired wound healing. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): CABOMETYX can cause RPLS. Perform evaluation for RPLS and diagnose by characteristic finding on MRI any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: CABOMETYX can cause thyroid dysfunction, primarily hypothyroidism, and it occurred in 19% of treated patients (0.4% Grade 3). Assess for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitor for signs and symptoms during treatment.

Hypocalcemia: CABOMETYX can cause hypocalcemia, with the highest incidence in DTC patients. Based on the safety population, hypocalcemia occurred in 13% of CABOMETYX patients (2% Grade 3 and 1% Grade 4).

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume CABOMETYX at a reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are:

CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, and constipation.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong or Moderate CYP3A4 Inducers: If coadministration with strong or moderate CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

Pediatric Use: Physeal widening has been observed in children with open growth plates when treated with CABOMETYX. Physeal and longitudinal growth monitoring is recommended in children (12 years and older) with open growth plates. Consider interrupting or discontinuing CABOMETYX if abnormalities occur. The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

Please see Important Safety Information and full Prescribing Information.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.