ASCO® Guidelines

Systemic Therapy for Tumor Control in Metastatic Well-differentiated Gastroenteropancreatic Neuroendocrine Tumors: ASCO Guideline				
Category	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
General recommendations for G1-G3 GEP-NETs	**1.1.** Selection of initial treatment options and sequencing of treatments following progression should consider patient and tumor characteristics such as hormone status, primary site, grade, extent and burden of disease, growth rate, comorbidities, and SSTR positivity, and should be discussed within a MDT when possible.	IC	L	S
	Note: • While local therapy options are outside the scope of this systematic review and guideline, surgical cytoreduction (if feasible to achieve > 70-90% reduction in tumor volume)[15] or other types of liver-directed therapy (e.g. embolization) may be considered for patients with hepatic disease, and preferably should be discussed within the setting of an MDT. • In addition, while the use of SSAs for symptom management is outside the scope of these guidelines, SSAs are often used indefinitely in patients with functional NETs.			
	1.2. All treatment decisions should be guided by a shared decision-making approach involving the patient, considering patient values and preferences, potential benefit and risk of harm, and patient characteristics and circumstances, which could include factors such as comorbidities, performance status, geographic location, and access to care.	IC	L	S
	1.3. Patients should be assessed for SSTR positivity using SSTR PET with ^{68}Ga-DOTA-peptides or ^{64}Cu-DOTATATE at baseline.	IC	L	S
First-line systemic therapy for G1-G2 GI-NETs	**2.1.** SSAs (octreotide or lanreotide) are recommended for SSTR-positive and/or functional metastatic G1-G2 GI-NETs.	EB	L	W
	Qualifying statements: • Observation and surveillance with anatomic imaging (CT or MRI) every 3-6 months, with extension to 6-12 months for patients with consistently stable disease, can be considered for patients with low volume metastatic G1-G2 GI-NETs, and an absence of symptoms from tumor burden or a functional tumor. For patients with bone-dominant metastases, follow-up with SSTR-PET imaging is recommended, due to the limited sensitivity of anatomical imaging for these metastases. • Evidence supporting SSA use for tumor control is strongest in patients with low or low-intermediate grade SSTR-positive tumors (Ki-67 <10%).			
	2.2. In the less common circumstance of patients with SSTR-negative G1-G2 GI-NETs, everolimus may be considered as a systemic treatment option.	EB	L	W

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Second- or later-line systemic therapy for G1-G2 GI-NETs	**2.3.** PRRT is recommended for patients with SSTR-positive metastatic G1-G2 GI-NETs that have progressed following treatment with SSAs.	EB	M	W
	Qualifying statements: • In addition to PRRT, continuation of treatment with SSAs is recommended for functional tumors; there is insufficient efficacy data to suggest that SSAs should be continued in patients with non-functional tumors at disease progression. • Patients with low volume of metastases should weigh the potential benefits of PRRT with the potential risk of long-term bone marrow toxicities.			
	2.4. Everolimus is recommended for patients with non-functional metastatic G1-G2 GI-NETs that are SSTR-negative, or SSTR-positive for whom PRRT is not an option due to higher risk of hematologic toxicity.	EB	M	W
	Qualifying statement: • Although the evidence base for everolimus is in patients with non-functional tumors, this agent may also be considered as later-line therapy for functional tumors.			
First-line systemic therapy for G1-G2 panNETs	**3.1.** SSAs (octreotide or lanreotide) are recommended for SSTR-positive and/or functional metastatic G1-G2 panNETs.	EB	L	W
	Qualifying statements: • Observation and regular anatomic imaging (CT or MRI) every 3-6 months, with extension to 6-12 months for patients with consistently stable disease, can be considered for patients with low volume metastatic G1-G2 panNETs, and an absence of symptoms from tumor burden or a functional tumor. For patients with bone-dominant metastases, follow-up with SSTR-PET imaging is recommended, due to the limited sensitivity of anatomical imaging for these metastases. • Evidence supporting SSA use for tumor control is strongest in patients with low or low-intermediate grade SSTR-positive tumors (Ki-67 <10%).			
	3.2. Chemotherapy (e.g. CAPTEM) is recommended for patients with G1-G2 higher volume panNETs and/or symptoms related to tumor burden.	EB	L	W
	Qualifying statement: • In the rare circumstance of patients with higher volume panNETs and/or symptoms related to tumor burden who are not candidates for chemotherapy, PRRT for patients with SSTR-positive tumors, or sunitinib or everolimus are recommended.			
	3.3. Chemotherapy (e.g. CAPTEM), everolimus, or sunitinib may be offered to SSTR-negative patients with G1-G2 panNETs.	EB	L	W
Second- or later-line systemic	**3.4.** PRRT for SSTR-positive tumors, chemotherapy (e.g. CAPTEM), everolimus, or sunitinib are recommended as second or later-line therapy for patients with G1-G2 panNETs, with choice of therapy depending on patient characteristics and goals of treatment.	EB	M	W

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therapy for G1-G2 panNETs	*Note:* • At this time, there is insufficient evidence to recommend a particular sequence of systemic therapy options following progression on SSAs for patients with G1-G2 panNETs; the order of options in Recommendation 3.4 is not intended to suggest a particular sequencing strategy**.**			
	Qualifying statements: • In addition to PRRT, continuation of treatment with SSAs is recommended for functional tumors; there is insufficient efficacy data to suggest that SSAs should be continued in patients with non-functional tumors at disease progression. • RCTs have not been published to date with PRRT in panNETs. • Patients with low volume of metastases should weigh the potential benefits of PRRT with the potential risk of long-term bone marrow toxicities. • Everolimus and sunitinib are cytostatic agents, and are associated with tumor stability, while chemotherapy and PRRT are associated with tumor response. • Comorbidities may be considered during selection of therapy; sunitinib is not recommended for patients with uncontrolled hypertension, and everolimus is not recommended for patients with uncontrolled diabetes.			
Systemic therapy for G3 GEP-NETs	**4.1.** The range of systemic options outlined in previous recommendations for G1-G2 NETs may be recommended for well-differentiated G3 GEP-NETs.	IC	VL	W
	Note: • G3 GEP-NETs are a relatively newly defined category within neuroendocrine neoplasms, and include a wide Ki-67 proliferation index range (i.e. >20%). Several trials, as outlined in the Discussion, are currently underway to inform specific therapy options, and may be used to inform recommendations for subpopulations of G3-NETs patients in the future.			
	Qualifying statements: • SSAs alone may be considered as first-line treatment in select cases (i.e. SSTR-positive, low volume of disease, low tumor-related symptom burden, less rapid rate of growth). • PRRT with or without SSAs is a potential treatment option for patients with SSTR-positive G3 GEP-NETs with characteristics such as less rapid rate of growth, and lower volume of disease who have progressed on SSAs alone. • Chemotherapy may be particularly effective for patients with characteristics such as higher proliferation index and/or mitotic rate, rapid rate of growth, and bulky disease. Evidence for cytotoxic chemotherapy is strongest for panNETs.			

Abbreviations. CAPTEM, capecitabine and temozolomide; CT, computed tomography; EB, evidence based; G, grade; GEP, gastroenteropancreatic; GI, gastrointestinal; H, high; IC, informal consensus; L, low; M, moderate; MDT, multidisciplinary team; MRI, magnetic resonance imaging; NETs, neuroendocrine tumors; pan, pancreatic; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; S, strong; SSAs, somatostatin analogs; SSTR, somatostatin receptor; W, weak