# Systemic Therapy for Tumor Control in Metastatic Well-differentiated Gastroenteropancreatic Neuroendocrine Tumors

## ASCO Guideline

Del Rivero & Perez et al.

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# 1 Background & Methodology

# Introduction

- Given the recent approval of several new therapies, members of ASCO identified a need for guidance on systemic treatment for metastatic GEP-NETs, particularly for clinicians in the community setting.
- This guideline focuses on strategies for controlling tumor growth in metastatic and advanced GEP-NETs.
- The control of hormonal syndromes in GEP-NETs will be addressed in a future ASCO guideline.
- Surgical therapy for NETs is beyond the scope of these guidelines on systemic therapies but plays an important role in the treatment of resectable NETs that are localized, with or without regional nodal disease, as well as in patients with metastases that can be effectively cytoreduced.[1] Similarly, liver-directed therapy also plays an essential role in the management of metastatic NETs to reduce tumor bulk and/or symptoms.[2]
- The choice of systemic therapy, surgery, or liver-directed therapy for individual NET patients is best made in the setting of an MDT.

# ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
  - a systematic literature review by ASCO guidelines staff
  - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  - final guideline approval by ASCO EBMC

- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

# Clinical Questions

This clinical practice guideline addresses three clinical questions:

1. What is the recommended initial and subsequent-line systemic treatment for G1-G2 GI-NETs?
2. What is the recommended initial and subsequent-line systemic treatment for G1-G2 panNETs?
3. What is the recommended systemic therapy for G3 GEP-NETs?

# Target Population and Audience

## Target Population

- Patients with well-differentiated metastatic G1-G3 GEP-NETs.

## Target Audience

- Medical oncologists, including community oncologists, nuclear medicine physicians, and other healthcare professionals who are involved in the care and treatment of patients with metastatic G1-G3 GEP-NETs.

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# 2 Summary of Recommendations

# Summary of Recommendations

## General Recommendations for G1-G3 GEP-NETs

## Recommendation 1.1

| Informal consensus<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| Low | Strong |

- 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 an MDT when possible.

*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)[3] 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.

# Summary of Recommendations

## Recommendation 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.

Informal consensus
benefits outweigh harms

| Evidence Quality | Strength of Recommendation |
|---|---|
| Low | Strong |

## Recommendation 1.3

- Patients should be assessed for SSTR positivity using SSTR PET with $^{68}$Ga-DOTA-peptides or $^{64}$Cu-DOTATATE at baseline.

Informal consensus
benefits outweigh harms

| Evidence Quality | Strength of Recommendation |
|---|---|
| Low | Strong |

# Summary of Recommendations

## First-Line Systemic Therapy for G1-G2 GI-NETs

## Recommendation 2.1

| Evidence-based<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| Low | Weak |

- SSAs (octreotide or lanreotide) are recommended for SSTR-positive and/or functional metastatic G1-G2 GI-NETs.

*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%).

# Summary of Recommendations

## Recommendation 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.

| Evidence-based<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| Low | Weak |

# Summary of Recommendations

## Second- or Later-Line Systemic Therapy for G1-G2 NETs

## Recommendation 2.3

| Evidence-based<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| Moderate | Weak |

- PRRT is recommended for patients with SSTR-positive metastatic G1-G2 GI-NETs that have progressed following treatment with SSAs.

*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.

# Summary of Recommendations

## Recommendation 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.

| Evidence-based<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| Moderate | Weak |

*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.

# Summary of Recommendations

## First-line Systemic Therapy for G1-G2 panNETs

## Recommendation 3.1

| Evidence-based<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| Low | Weak |

- SSAs (octreotide or lanreotide) are recommended for SSTR-positive and/or functional metastatic G1-G2 panNETs.

*Qualifying statements:*

- Observation and regular anatomic imaging (computed tomography (CT) or magnetic resonance imaging (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%).

# Summary of Recommendations

## Recommendation 3.2

- Chemotherapy (e.g. CAPTEM) is recommended for patients with G1-G2 higher volume panNETs and/or symptoms related to tumor burden.

| Evidence-based<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| Low | Weak |

*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.

## Recommendation 3.3

- Chemotherapy (e.g. CAPTEM), everolimus, or sunitinib may be offered to SSTR-negative patients with G1-G2 panNETs.

| Evidence-based<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| Low | Weak |

# Summary of Recommendations

## Second- or Later-Line Systemic Therapy for G1-G2 panNETs

## Recommendation 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.

| Evidence-based<br>benefits outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| Moderate | Weak |

*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 on next slide.*

# Summary of Recommendations

*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.

# Summary of Recommendations

## Systemic Therapy for G3 GEP-NETs

## Recommendation 4.1

| Informal consensus<br>benefits may outweigh harms | |
|---|---|
| **Evidence Quality** | **Strength of Recommendation** |
| Very Low | Weak |

- The range of systemic options outlined in previous recommendations for G1-G2 NETs may be recommended for well-differentiated G3 GEP-NETs.

*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 on next slide.*

# Summary of Recommendations

*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

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# 3 Discussion

# Discussion

- There is currently insufficient evidence available to inform recommendations for sequencing of recommended therapy options, particularly following progression. Some recommendations were informed by indirect evidence.
- In addition, there was little data available data to inform treatment options for G3 GEP-NETs.
- As such, and because of several options available for subpopulations of patients, the recommendations are labeled weak according to the GRADE criteria, which means that the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists; most informed people would choose the recommended course of action, but a substantial number would not.
- Qualifying statements are provided to assist with treatment choice and implementation of the recommendations.
- This guideline will be updated as newer evidence from trials in progress becomes available.

# Patient and Clinician Communication

- An overarching guideline recommendation is included for a shared decision-making approach involving the patient, taking into account their values and preferences, potential benefit and risk of harm, and specific characteristics and circumstances.
- Patient-clinician communication is important in the era of radiology reports being directly visible to patients through secure portals and it is important to have clarity in the description and interpretation of somatostatin receptor avidity.
  - The SUV is a semi-quantitative measurement prone to variation based on isotope preparation and time to delivery, among other factors, such that it has only limited utility “in comparing tumor biological differences among patients and treatment response assessment.”[4]
  - As such, a higher SUV on one scan compared to prior imaging does not denote progression in and of itself.
- When considering treatment with PRRT for patients with the risk factors for serious hematological toxicity outlined previously, clinicians should discuss the risk of treatment-related myelodysplastic neoplasia with their patients, and should have a low threshold for investigating persistent cytopenia or macrocytosis.[5]

# Health Disparities

- Many patients have limited access to medical care or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation and gender identity, geographic location, and insurance access are known to impact cancer care outcomes.[6]
- Medicaid does not pay for SSTR-PET in some places in the US.
- Outside the US, access to recommended treatments can be limited or variable.
  - For example, in many countries, the SSA lanreotide is not available, and there is a lack of coverage for drugs such as sunitinib.
- Awareness of these disparities in access to care should be considered in the context of this guideline, and providers should strive to deliver the highest level of care to these vulnerable populations, and populations with limited access to the recommended therapy options.
- Stakeholders should work towards achieving health equity by ensuring equitable access to both high-quality cancer care and research and addressing the structural barriers that preserve health inequities.[6]

# Cost Implications

- Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs. Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended treatments.
- Discussion of cost can be an important part of shared decision-making.
- Anecdotally, some Expert Panel members report that reimbursement for SSTR-PET may be limited in some areas of the US.
- There may also be a cost associated with acquiring the knowledge, skills, and staff to successfully incorporate PRRT into clinical practice. There can also be a significant financial burden for patients with indefinite longitudinal treatments like monthly SSA injections.[7-12]
- Review articles that have attempted to quantify the financial impact of NETs have found significant gaps in the literature on resource use, cost, economics, and budget impacts associated with neuroendocrine tumors and call for more research in this area to aid the decision-making process for patients with NETs.[12]

# Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines

- Patient information is available at www.cancer.net

# Guideline Panel Members

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# Guideline Panel Members

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# Abbreviations

- ASCO, American Society of Clinical Oncology
- CAPTEM, capecitabine and temozolomide
- CT, computed tomography
- EBMC, Evidence Based Medicine Committee
- GEP, gastroenteropancreatic
- G, grade
- GI, gastrointestinal
- MDT, multidisciplinary team
- MRI, magnetic resonance imaging
- NETs, neuroendocrine tumors
- pan, pancreatic
- PET, positron emission tomography
- PRRT, peptide receptor radionuclide therapy
- SSAs, somatostatin analogs
- SSTR, somatostatin receptor
- SUV, standardized uptake value
- US, United States

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