SOMATOSTATIN ANALOGS

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DISCLOSURE OF INTEREST

- **Personal financial interests:** Novartis, Ipsen, Pfizer, Merck Serono, Advanced Accelerator Applications, MSD (Advisory board, public speaking)

- **Institutional financial interests:** Novartis, Ipsen, Merck Serono, MSD, Pharmacyclics, Incyte, Halozyme, Roche, Astellas, Pfizer (Clinical trial or research projects: principal investigator, steering committee member)

- **Non-financial interests:**
  - ESMO: Coordinator of the Neuroendocrine, Endocrine neoplasms and CUP Faculty
  - ENETS: advisory board chairman
  - AIOM: coordinator for ITALIAN NEN guidelines
  - ITANET: Scientific committee member
First report of SST efficacy on carcinoid syndrome

SST discovery

Octreotide s.c. commercialization

Octreotide synthesis

Lanreotide commercialization

OCT LAR FDA approval

Lanreotide ATG introduction

SSTR 1-5 identification

Pasireotide introduction


Thulin L et al. Lancet. 1978
Frolich JC et al., N Engl J Med. 1978
Therapies for patients with advanced NETs

- **Octreotide / IFN in carcinoid syndrome**
- **Lanreotide in carcinoid syndrome**
- **Octreotide in NF midgut**
- **Lanreotide in NF GEP**
- **Pasireotide**

- FDA/EMA Approved
- Not FDA/EMA approved
## Octreotide and Lanreotide formulations

<table>
<thead>
<tr>
<th>Octreotide short acting s.c. (mg x 1-3/day)</th>
<th>Octreotide LAR I.M. (mg/4w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>10</td>
</tr>
<tr>
<td>0.1</td>
<td>20</td>
</tr>
<tr>
<td>0.2</td>
<td>30</td>
</tr>
<tr>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Lanreotide microparticles I.M. (mg/2 w)</th>
<th>Lanreotide autogel deep s.c. (mg/4w)</th>
</tr>
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<tbody>
<tr>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>60</td>
<td>90</td>
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<tr>
<td></td>
<td>120</td>
</tr>
</tbody>
</table>
Somatostatin receptors (SSTRs)

Up to 60% of homology

<table>
<thead>
<tr>
<th>Function</th>
<th>SSTR1</th>
<th>SSTR2</th>
<th>SSTR3</th>
<th>SSTR4</th>
<th>SSTR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone secretion</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Proliferation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Apoptosis</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

De Herder et al., End Rel Cancer 2003
Somatostatin (SST)

Octreotide, Lanreotide (SSAs)

Octreotide and lanreotide bind mainly to SSTR-2 and 5

Pasireotide

sst₁  sst₂  sst₃  sst₄  sst₅

Somatostatin (SST)
Subtype-2 somatostatin receptor (SSTR-2)
**SSTR-2 IHC score**

<table>
<thead>
<tr>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
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</table>

**SUBCELLULAR PATTERN**

- (Negative)
- Pure cytoplasmic
- Membranous usually incomplete
- Membranous circumferential

**EXTENSION OF POSITIVE TUMOR CELL POPULATION**

- (Absent)
- 1-100% <50% >50%

**CONCORDANCE WITH OCTREOSCAN DATA**

| 50% | 54% | 87% | 94% |
SSA in SSTR-2 negative context: ENETS guidelines

“SSA may be considered in somatostatin receptor (SSTR) negative NEN if small volume disease is present and it is expected that imaging may have provided falsely negative information on SSTR status. Immunostaining with SSTR2 antibodies may also be useful.”

Pavel et al., Neuroendocrinology 2017
SS analogs: mechanisms of antiproliferative action

SSAs

DIRECT (receptor-dependent)
  - Cell cycle
  - GFs
  - Apoptosis

INDIRECT (receptor-independent)
  - GF and trophic hormone release
  - Immune system
  - Angiogenesis
Somatostatin (SST)
(somatotropin release-inhibiting factor, SRIF)

GI tract (endocrine)
- Gastrin
- VIP
- Secretin
- CCK
- Insulin
- Glucagon

GI tract (exocrine)
- Gastric acids
- Intestinal fluids
- Pancreatic enzymes
- GI motility
- Gallbladder contraction
- Portal blood flow

Paragliola et al., Drug Des Devel Ther 2016
Octreotide / Lanreotide side effects

Acute:
abdominal pain, diarrhea, steatorrhea, headache, local pain, nausea, hypoglycaemia

Chronic:
cholelithiasis, hyperglycaemia, hypothyroidism, hyperbilirubinaemia, hypovitaminosis B
Dose of SSAs: debated point

Blood level is correlated to:

- BMI
- Concurrent therapies
- Gender
- Status of the tumor

Around half of pts required rescue at all dose levels

SSTR-2 saturation occurred with OCT LAR 60 mg q4w

Rubin, JCO 1999
Wolterting, Pancreas 2005
SSAs in carcinoid syndrome-associated NETs
## SSA in Carcinoid syndrome: 2018 NCCN guidelines

<table>
<thead>
<tr>
<th>CARCINOID SYNDROME</th>
<th>TREATMENT</th>
<th>SURVEILLANCE</th>
</tr>
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<tbody>
<tr>
<td>EVALUATION</td>
<td></td>
<td></td>
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<tr>
<td>Recommended:</td>
<td>Octreotide&lt;sup&gt;o,hh,ii&lt;/sup&gt; or lanreotide&lt;sup&gt;o,hh&lt;/sup&gt;</td>
<td>Echocardiogram every 2–3 y or as clinically indicated</td>
</tr>
<tr>
<td>• Biochemical evaluation with 24-hour urine or plasma 5-HIAA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Carcinoid syndrome well controlled</td>
<td>• Abdominal/pelvic multiphasic CT or MRI every 3–12 mo, and chest CT (± contrast) as clinically indicated</td>
</tr>
<tr>
<td>• Echocardiogram</td>
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<tr>
<td>• Imaging to assess disease progression (See NET-8 or NET-10)</td>
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**ELECT** prospective study

Pts with NET and stable carcinoid syndrome

Interactive voice/web response syndrome

115 rand. pts

- 51 OCT naive
- 64 prior OCT

26 LAN 120/4w

- 25 PLB
- 26 LAN 120/4w
- 25 PLB

- Less s.c. OCT rescue in LAN than PLB
- Lower % of days with diarrhea and/or flushing in LAN than PLB

*Fisher et al., Endocr Practice 2018*

*Vinik et al., Endocr Practice 2016*
SSA in Carcinoid syndrome: 2018 NCCN guidelines

NCCN Guidelines Version 2.2018
Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

CARCINOID SYNDROME
EVALUATION

Recommended:
- Biochemical evaluation with 24-hour urine or plasma 5-HIAA\textsuperscript{b}
- Echocardiogram
- Imaging to assess disease progression (See NET-8 or NET-10)

TREATMENT

Carcinoid syndrome well controlled

Octreotide\textsuperscript{0,hh,h} or lanreotide\textsuperscript{0,hh}

Carcinoid syndrome poorly controlled

For any persistent symptoms (ie, flushing, diarrhea) consider additional therapy for disease control:
- Consider hepatic arterial embolization ± cytoreductive surgery for hepatic predominant disease
- Consider telotristat (250 mg, by mouth 3 times a day)\textsuperscript{ll}
  or
- Consider other systemic therapy based on disease site\textsuperscript{0,kk}

SURVEILLANCE

• Echocardiogram every 2–3 y or as clinically indicated
• Abdominal/pelvic multiphasic CT or MRI every 3–12 mo, and chest CT (± contrast) as clinically indicated
SSA in Carcinoid syndrome: 2016 ENETS guidelines

Minimal consensus statement: Somatostatin analogs, octreotide and lanreotide, are effective drugs for syndrome control in functional NET. In refractory carcinoid syndrome or insufficient syndrome control in pancreatic NET, dose escalation of SSA may be recommended. The novel somatostatin analogs, pasireotide, are considered an alternative treatment option.

Pavel et al, Neuroendocrinology 2016
SSAs in functioning NET: clinical practice

With octreotide at 30 mg/4w

- up to 40% of pts require s.c. rescue
- up to 40% of pts receive > 30 mg/4w (above label-dose)
Gastrointestinal neuroendocrine tumors treated with high dose octreotide-LAR: A systematic literature review

- Systematic literature review
- 17 studies
- 260 pts on SSA
- SSA dose from 20-30 mg / 3-4 w → 120 mg / 4 w

“Above-label doses of octreotide-LAR are being used frequently for the management of NETs in clinical practice and excess toxicity has not been observed “

Broder et al, World J Gastroenterol 2015
SSA above-label dose in NETs

Patients Treated with Octreotide LAR (n=338)

- Above-label Doses (n=100)
  - Refractory Syndrome (n=60)
  - Radiographic Tumor Progression (n=33)
- Standard Dose Levels (n=228)
  - Rising Levels of Urine 5-HIAA (n=6)
  - Unknown Reason For Increase (n=1)

Strosberg et al., Gastrointest Cancer Res 2013
Carcinoid syndrome: therapies

1. SSA Label-dose
   - Refractory carcinoid syndrome

2. SSA dose/schedule modulation
   - Tumor progression

3. Telotristat (if diarrhea)
   - Liver-directed treatments
   - PRRT
   - EVE
SSA in carcinoid syndrome: Some issues

- Starting dose
- Full dose
- Definition of refractory carcinoid syndrome on SSA treatment
SSAs in non functioning NETs
SSA indications in NETs

Tumor growth control
## Octreotide and lanreotide antiproliferative activity and efficacy in advanced GEP NETs

<table>
<thead>
<tr>
<th>Decade</th>
<th>Description</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s</td>
<td>SSAs stabilised progressing tumors</td>
<td>Clinical observations</td>
</tr>
<tr>
<td>1990s</td>
<td>SSA provides antitumour activity (SD, PR) in progressive GEP NET in retrospective or prospective studies including two randomized studies</td>
<td>Low-level evidence</td>
</tr>
<tr>
<td>2000s</td>
<td>Randomised phase III PLB-controlled trials: PROMID, CLARINET</td>
<td>High-level evidence</td>
</tr>
</tbody>
</table>
PROMID / CLARINET: period of enrollment
SSA as antitumor therapy in GEP NETs: Rand. Phase III trials

**PROMID**

Small bowel
Octreotide LAR 30 mg q4w

Primary endpoint: TTP

- Placebo, 40 events; median, 6.0 months
- Octreotide LAR, 26 events; median, 14.3 months

TTP = 14 vs 6 mo

HR=0.34; 95% CI: 0.20–0.59; \(P=0.000072\)

*Rinke et al., JCO Oct 2009*

**CLARINET**

Enteropancreatic
Lanreotide autogel 120 mg q4w

Primary endpoint: PFS (ITT population, N=204)

- Lanreotide Autogel 120 mg: 32 events / 101 patients median, not reached
- Placebo: 60 events / 103 patients median, 18.0 months [95% CI: 12.1, 24.0]

Lanreotide Autogel vs. placebo

\(p=0.0002\)

HR=0.47; 95% CI: 0.30–0.73; \(P=0.0002\)

*Caplin NEJM 2014*
Many RECIST-based stable tumors at baseline were growing in fact. At baseline 96% of tumors were stable according to RECIST.
Tumor growth rate (TGR)

A) TGR<sub>0</sub> ≤ 4% per month

- Lanreotide 120 mg, median PFS not reached.
- Placebo, median PFS 97.7 weeks [95% CI: 72.1–not reached].

Hazard ratio: 0.27 [95% CI: 0.12–0.60]; p < 0.001

B) TGR<sub>0</sub> > 4% per month

- Lanreotide 120 mg, median PFS 96.3 weeks [95% CI: 37.1–not reached].
- Placebo, median PFS 37.7 weeks [95% CI: 36.1–48.3].

Hazard ratio: 0.37 [95% CI: 0.20–0.69]; p = 0.001
Midgut well differentiated NET: SSA as first-line therapy

- **Octreotide LAR 30 mg/4w**
- **Lanreotide autogel 120 mg/4w**

**PROMID trial**
- SSTR +++
- Ki-67 < 3%

**CLARINET trial**
- Ki-67 < 11% (70% < 3%)
- SSTR +++
SSA in PanNET: a class-effect activity?

NCCN Guidelines Version 1.2015
Neuroendocrine Tumors of the Pancreas

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES^

Locoregional unresectable disease and/or Distant metastases

If complete resection possible^,t

Resect metastases + primary^u

Clinically significant progressive disease, see below

Asymptomatic, low tumor burden, and stable disease

• Observe with markers and scans every 3–12 mo
• Consider treatment with octreotide^,v or lanreotide^,v

Clinically significant progressive disease, see below

Symptomatic or Clinically significant tumor burden or Clinically significant progressive disease

Manage clinically significant symptoms as appropriate (PanNET-1, PanNET-2, PanNET-3, PanNET-4, and PanNET-5)

Consider octreotide^,v or lanreotide^,v if not already receiving and/or
• Everolimus\(^l\) (10 mg/d)
• Sunitinib\(^l\) (37.5 mg/d)
• Cytotoxic chemotherapy\(^l\)
• Hepatic regional therapy (ie, arterial embolization, chemoembolization, radioembolization [category 2B])
• Cytoreductive surgery/ablative therapy\(^m\) (category 2B)
**Minimal consensus statement:** Somatostatin analogs, octreotide and lanreotide, are effective drugs for syndrome control in functional NET. In refractory carcinoid syndrome or insufficient syndrome control in pancreatic NET, dose escalation of SSA may be recommended. The novel somatostatin analog, pasireotide might be considered in refractory carcinoid syndrome in case all other treatment options including ablative procedures, TAE and interferon alpha have failed, and there is no clinical trial available. If approved, the oral serotonin synthesis inhibitor telotristat etiprate will offer a novel treatment option in refractory carcinoid syndrome. For antiproliferative purpose, SSA may be used in stable or progressive disease or in patients with unknown tumor behaviour. SSA are recommended first-line therapy in midgut NET and can be considered in pancreatic NET as a first-line therapy (up to a Ki67 of 10%). While the antiproliferative efficacy of both available SSA is considered a class effect, there is a higher level of evidence for the use of lanreotide AG in pancreatic NET, and based on the respective study designs octreotide LAR is approved for tumor control in midgut NET whereas lanreotide AG is approved for enteropancreatic NET. SSA may be considered in low grade NET of other sites. There is no established Ki-67 threshold for the use of SSA, preferably SSA should be used if Ki-67 is ≤ 10%.

*Pavel et al, Neuroendocrinology 2016*
SSA as antiproliferative therapy in advanced Pancreatic NETs
ENETS 2016 guidelines

Pavel et al, Neuroendocrinology 2016
SSA as antiproliferative therapy in advanced midgut NETs

ENETS 2016 guidelines

Pavel et al, Neuroendocrinology 2016
CLARINET post-hoc analysis:
Impact of Lanreotide on plasma CgA and urine HIAA

CLARINET trial (all pts with non functioning NETs)
Baseline >UNL blood CgA 48%
Baseline >UNL urine HIAA 66% (26% PanNET)

Pavel et al., Oncologist 2018
Predictive factors of response to SSAs

Predictive of better tumor response at multivariate analysis:

- Male sex
- Carcinoid heart disease
- Baseline SD

Laskaratos et al., Br J Cancer 2016
SSA combined with other therapies
NETTER-1 trial (229 patients)

Strosberg et al., NEJM 2017
PRRT + concomitant and/or maintenance SSA

Group 1: PRRT alone (81 pts)
Group 2: PRRT + SSA (77% OCT, 23% LAN) → SSA as maintenance

Survival benefit was seen in both functioning and non-functioning NETs

Yordanova et al, Clin Cancer Res 2018
SSA combined with molecular targeted agents

**EVEROLIMUS + SSA**

- Phase II: Yao et al., 2008
- RADIANT-1: Yao et al., 2008
- RADIANT-3: Yao et al., 2011
- Phase II 1st line: Bajetta et al., 2013

**Sunitinib + SSA**

- Phase III: Raymond et al., 2011
- Retrospective: Capdevila BMC Cancer 2015
- SUNLAND: ongoing
SSA + Metronomic chemotherapy in NETs: Phase II trials

- OCT LAR + mCAP
- OCT LAR + 5-FU P.V.I.
- OCT LAR + mTMZ
Lanreotide + Temozolomide: SONNET trial

57 German patients with advanced pre-treated G1-2 GEP or UP NETs

- DCR (SD+PR+CR) = 73%
  (62% pancreas, 77% intestinal)
- Maintenance therapy with LAN prolonged disease control
- Median PFS = 11 months

Pavel et al, ENETS 2018 Poster
Lanreotide + Temozolomide: ATLANT trial

47 Italian patients with Advanced pre-treated lung/thymus NETs

✓ 36 lung + 4 thymus

✓ SSTR-2 + at the functional imaging

✓ Primary endpoint: 9-month PFS (pending results)

Ferolla et al, ENETS 2019 Poster
CONCLUDING REMARKS

- SSAs are the recommended first-line therapy for carcinoid syndrome NET patients.
- SSAs are recommended for patients with non-functioning, slow-growing, low-grade advanced GEP and lung NETs.
- SSA are not recommended for adjuvant therapy and for high grade NECs.
- SSA continuation in non-functioning progressing advanced NET patients is a debated point.