Recommendations for the management of small bowel NET

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Disclosure

- Honoraria for presentations from Novartis, IPSEN, Pfizer, Lexicon
- Honoraria for participation in advisory boards from Novartis, IPSEN, Pfizer, Lexicon
Overview

- Epidemiology and clinical presentation
- Therapeutic options
  - Syndrome control
  - Tumor control
- Therapy algorithm (ESMO*/ ENETS** consensus guidelines)
- Clinical trials

Inidence of Neuroendocrine Tumors: systematic review

Small intestine NET

Fraenkel et al, Endocr Related Cancer 2014
Intestinal NET

- Most intestinal NET are metastatic at time of diagnosis
- The majority are non-functioning NET
- 10-30% are associated with the carcinoid syndrome (flush/diarrhea); ~40% develop carcinoid heart disease
- The majority (57-95%) are G1 NET (<2% Ki67)
- Most tumors (~90%) express SSTR-2
- Functionality and grade guide therapeutic decision making

Small Bowel NET
Clinical presentation

- Bleeding
- Peritoneal carcinomatosis
- Carcinoid Heart Disease
- Carcinoid Syndrome
- Carcinoid Crisis

Small bowel obstruction
Mesenterial LN + Fibrosis
Liver Metastases

Tumor growth / spread
Functionality
Treatment goals

- Prevent and treat local tumor related complications
- Syndrome control & prevention of sequelae; treatment of carcinoid heart disease
- Inhibition of tumor growth (metastases)
Resection of primary tumor in distant metastatic disease?

Resection of primary tumor (intestine) and impact on prognosis

249 primary resected, MS = 7.4 y

Hellman et al, 2002
Givi et al, 2006
Ahmed et al, 2009
Rinke et al 2009
Survival after resection of liver metastases
Consensus Conference, London 2012

Limitations

Complete resection in 20–57%.

Recurrence in up to 94% after 5 years.*

No randomized trials.
Management of liver metastases without extrahepatic disease

ENETS Guidelines 2012

Morphological & Functional Imaging

- Resection of primary
- No extrahepatic spread

A. Simple pattern of LMs G1/G2 (unilobar or limited)
  - Resection (minor or anatomical)
  - Surgery contraindicated

B. Complex pattern of LMs G1/G2 (bilobar)
  - One-step surgery
    - Major liver resection ± RFA
  - Two-step surgery
    - 1. Minor resection ± RFA, RPVE, RPVL
    - 2. Sequential major liver resection

C. Diffuse LMs G1/G2
  - Or surgery contraindicated

Midgut NET
- Somatostatin Analogs
- Interferon
- PRRT
- Everolimus
- (Chemotherapy)
- Novel drugs

NEC G3: platinum-based systemic Chemotherapy - 1st line

Pavel et al., Neuroendocrinology, 2012
Systemic Therapy Options

- „Biotherapy“ („targeted therapy“)
  - Somatostatin analogs
  - Alpha-Interferon
  - Novel therapies (Clinical trials)

- Novel molecular targeted therapies
- Peptide receptor radionuclide therapy/PRRT
- Systemic Chemotherapy
Symptom relief in carcinoid syndrome by Somatostatin analogs

Symptomatic response (%)

- **Octreotide**: Mean: 74.2, Median: 71
- **Octreotide LAR**: Mean: 77.3, Median: 75
- **Lanreotide**: Mean: 63.0, Median: 63
- **Lanreotide slow release / autogel**: Mean: 67.5, Median: 63

Studies (n) | Patients (n)
--- | ---
11 | 261
7 | 122
1 | 30
7 | 185

Interferon-alpha in NET

**Response**
- **IFN**: 40-70%
- **PEG-IFN**: ca. 40%

**Symptoms**
- **IFN**: 70%
- **PEG-IFN**: 12%

**Bio**
- **IFN**: 3x3
- **PEG-IFN**: 50-100µg/wk

**Tumor**
- **IFN**: 3x5Mio IU/wk
- **PEG-IFN**:

**Dose**

**Response**

**IFN**
- Öberg et al 1983, Moertel et al 1989
- Arnold et al 2005

**PEG-IFN**
- Pavel et al 2006

SSA are first-line therapy for syndrome control. IFN is of value as add-on therapy in refractory CS in selected patients.
Therapeutic options in refractory carcinoid syndrome

**Somatostatin analogs**
- Octreotide LAR 10-30 mg /mo
- Lanreotide AG 60-120 mg /mo

Dose escalation

- + Interferon alpha
- Disease restricted to the liver
  - Or SRS negative

- Peptide Receptor Radionuclide Therapy
  - SRS positive
  - + Progression

**Exclude other causes**
- of diarrhea, e.g.
  - Bile acid loss
  - Pancreatic enzyme insufficiency

**Chemo/-Embolisation**
- HFTT; RFA; Debulking

Novel somatostatin analogs: Pasireotide (not approved)

Clinical trial: e.g. Telotristat Etiprate?
Telotristat Etiprate (LX1606)- an oral serotonin synthesis inhibitor

- Dose escalation study (Phase II) to assess the
- Efficacy and Safety of LX1606 in
- Patients with symptomatic Carcinoid Syndrome
  (Germany & UK)

5-HIAA:
-71.9% change from baseline at Wks 11-12

Sponsor: Lexicon Pharmaceuticals
Tumor control
Natural tumor biology of intestinal NET Systemic Disease

Therapeutic Options

<table>
<thead>
<tr>
<th>Grading (Ki67)</th>
<th>Watch &amp; wait</th>
<th>Somatostatin analogs</th>
<th>Interferon-alpha</th>
<th>PRRT</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67 &lt; 2%</td>
<td>stable</td>
<td>slowly growing</td>
<td>fast growing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Charité Campus Virchow-Klinikum
Therapeutic options in intestinal NET

- Surgical resection
- Loco-regional and ablative procedures
- Somatostatin analogs
- Peptid-Receptor Radionuclide Therapy (PRRT)
- Molecular targeted therapy (Everolimus)
- Systemic Chemotherapy

Placebo-controlled Studies
## Somatostatin Analogs
### Antiproliferative Efficacy

**Table 2. Antiproliferative Effect of Somatostatin Analogs in Patients With Progressive Disease**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>SA</th>
<th>SD %</th>
<th>PR/CR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold et al(^{44})</td>
<td>52</td>
<td>Octreotide</td>
<td>36</td>
<td>3%</td>
</tr>
<tr>
<td>Saltz et al(^{45})</td>
<td>34</td>
<td>Octreotide</td>
<td>50</td>
<td>—</td>
</tr>
<tr>
<td>di Bartolomeo et al(^{46})</td>
<td>58</td>
<td>Octreotide</td>
<td>46</td>
<td>PR: 3</td>
</tr>
<tr>
<td>Ricci et al(^{47})</td>
<td>15</td>
<td>Octreotide</td>
<td>40</td>
<td>PR: 7</td>
</tr>
<tr>
<td>Aparicio et al(^{48})</td>
<td>35</td>
<td>Octreotide/lanreotide</td>
<td>57</td>
<td>PR: 3</td>
</tr>
<tr>
<td>Faiss et al(^{49})</td>
<td>30</td>
<td>Lanreotide</td>
<td>37</td>
<td>PR: 3.3</td>
</tr>
<tr>
<td>Faiss et al(^{50})</td>
<td>25</td>
<td>Lanreotide</td>
<td>28</td>
<td>PR: 4</td>
</tr>
<tr>
<td>Ducreaux et al(^{51})</td>
<td>39</td>
<td>Lanreotide</td>
<td>48.7</td>
<td>PR: 5</td>
</tr>
<tr>
<td>Bianchi et al(^{52})</td>
<td>23</td>
<td>Lanreotide autogel</td>
<td>65.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Massuti et al(^{53})</td>
<td>30</td>
<td>Lanreotide autogel</td>
<td>88.9</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Abbreviations: SA, somatostatin analogs; SD, stable disease; PR, partial response; CR, complete response.

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Review: Toumpanakis & Caplin Semin Oncol 2013
Placebo-controlled trials with SSA in advanced NET to assess antiproliferative efficacy

A randomized double-blind placebo-Controlled study of Lanreotide Antiproliferative Response In patients with gastroenteropancreatic NeuroEndocrine Tumors (CLARINET)

Martyn Caplin,1 Philippe Ruszniewski,2 Marianne Pavel,3 Jarosław Ćwikła,4 Alexandria Phan,5 Markus Raderer,6 Eva Sedláčková,7 Guillaume Cadiot,8 Lucy Wall,9 Guido Rindi,10 Nilani Liyanage,11 Joëlle Blumberg,11 on behalf of the UK & Ireland Neuroendocrine Tumor Society, the European Neuroendocrine Tumor Society, and CLARINET Investigators

84 patients with midgut NET

204 patients with entero-pancreatic NET
# PROMID & CLARINET
Comparison of study designs

<table>
<thead>
<tr>
<th></th>
<th>PROMID Study</th>
<th>CLARINET Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSA Dose</td>
<td>Octreotide LAR 30 mg</td>
<td>Lanreotide AG 120 mg</td>
</tr>
<tr>
<td>Patient population</td>
<td>Midgut</td>
<td>Entero-pancreatic</td>
</tr>
<tr>
<td>Functionality</td>
<td>+/-</td>
<td>Non-functioning</td>
</tr>
<tr>
<td>Response assessment</td>
<td>WHO</td>
<td>RECIST</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>TTP</td>
<td>PFS</td>
</tr>
<tr>
<td>Disease status</td>
<td>Unknown</td>
<td>SD (95%)</td>
</tr>
<tr>
<td>Ki67</td>
<td>&lt; 2 % (95%)</td>
<td>&lt;2% (68%) &lt;10% (32%)</td>
</tr>
<tr>
<td>Liver involvement</td>
<td>&lt; 10% (77%)</td>
<td>&lt;10% (49%) &gt;25% (39%)</td>
</tr>
</tbody>
</table>
PROMID Study: Octreotide LAR 30 mg vs Placebo in Midgut NET

Time to progression (WHO)

Octreotide LAR is standard treatment for patients with functioning and nonfunctioning, well differentiated, small intestine (midgut) NET. May be considered in NET G1 of other sites NET (ENETS/ ESMO/ NCCN Guidelines).

Octreotide vs. Placebo
SD in 66.7% vs. 37.2% at 12 months

Watch & wait? vs early therapy onset

Primary endpoint: PFS (ITT, n=204)

Lanreotide Autogel vs. placebo
p=0.0002 HR=0.47 [95% CI: 0.30, 0.73]

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]

Overall survival
19 vs. 17 deaths
(n.s.)

P-value derived from stratified log-rank test; HR derived from Cox proportional hazards model. HR, hazard ratio; ITT, intention-to-treat.

Caplin et al, ESMO Annual Meeting Amsterdam 2013
Progression free Survival Lanreotide AG vs Placebo in Midgut NET (subgroup analysis)

Midgut NETs (n=73)
Lanreotide Autogel vs. placebo
P=0.0091 HR=0.35 [95% CI: 0.16, 0.80]

- **Lanreotide Autogel 120 mg**
  - 8 events / 33 patients
  - Median, not reached

- **Placebo**
  - 21 events / 40 patients
  - Median, 21.1 months [95% CI: 17.0, NC]

P-value derived from log-rank test; HR derived from Cox proportional hazards model. NC, not calculable.

Caplin et al, ESMO Annual Meeting Amsterdam 2013
## CLARINET Subgroup Analysis by Ki67 and hepatic tumor load

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Median Progression free survival (PFS)</th>
<th>Statistical results</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO grade tumors: G1 (n=141)</td>
<td>• Lanreotide AG &gt; 27 months</td>
<td>• HR 0.43</td>
</tr>
<tr>
<td></td>
<td>• Placebo: 18.3 months</td>
<td>• 95% CI: 0.25 -0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• p=0.0016</td>
</tr>
<tr>
<td>WHO grade tumors: G2 (n=61)</td>
<td>• Lanreotide AG &gt; 27 months</td>
<td>• HR 0.45</td>
</tr>
<tr>
<td></td>
<td>• Placebo: 12.1 months</td>
<td>• 95% CI: 0.22 -0.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• p=0.0235</td>
</tr>
<tr>
<td>Hepatic tumor load (≤ 25%) (n=133)</td>
<td>• Lanreotide AG &gt; 27 months</td>
<td>• HR 0.34</td>
</tr>
<tr>
<td></td>
<td>• Placebo: 21.1 months</td>
<td>• 95% CI: 0.18 -0.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• p=0.0002</td>
</tr>
<tr>
<td>Hepatic tumor load (&gt; 25%) (n=67)</td>
<td>• Lanreotide AG: 24.1 months</td>
<td>• HR 0.45</td>
</tr>
<tr>
<td></td>
<td>• Placebo: 9.4 months</td>
<td>• 95% CI: 0.23 - 0.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• p=0.0170</td>
</tr>
</tbody>
</table>

Caplin et al, ESMO Annual Meeting Amsterdam 2013; ESMO Press Release Sept 2013
## Tolerability of Somatostatin Analogs

- **Diarrhoea**: 37.3%
- **Steatorrhoea**: 39.3%
- **Flatulence**: 28.1%
- **Pain at injection site**: 28.1%
- **Gall stones**: 17.9%
- **Emesis**: 11.5%
- **Hyperglycaemia**: 10.8%
- **Bradycardia**: 4.3%
- **Cholangitis**: 4.3%
- **Septicaemia**: <1%

### Notes:
- Most side effects are transient
- 30 years of experience
- Very good long-term tolerability

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Any value of novel targeted drugs in intestinal NET?
Targeted Drugs in Neuroendocrine Tumors

- **Novel Somatostatin analogues:**
  Pasireotide (SOM230), chimeric molecules (e.g. Dopastatin)

- **Others:** Tryptophan hydroxylase inhibitor (**Telotristat Etiprate**, **LX1606**), IGF-1 R antagonists/antibodies, HDAC inhibitors etc

- **Angiogenesis inhibitors:**
  VEGF-Receptor-Tyrosinkinase-Inhibitor PTK787/ZK, Anti-VEGF (**Bevacizumab**), Endostatin, Thalidomide

- **Single / multiple tyrosine kinase inhibitors:**
  Imatinib, Gefitinib, Sorafenib, **Sunitinib**

- **mTOR Inhibitors:** Temsirolimus, **Everolimus**
Everolimus in non-pancreatic NET / Carcinoids?

RADIANT-2 Study

Everolimus + Octreotide

PFS (E+O) 16.4 mo.
PFS (P+O) 11.4 mo.

ENETS Guidelines: Everolimus may be considered in intestinal NET if other treatments failed
(no approval, potential side effects)

429 patients: 51% small intestine, 15% lungs, 7% colon; 5% pancreas

Sunland Study
Lanreotide vs. Lanreotide + Sunitinib

Sunitinib in carcinoids
N= 41 pts, Kulke et al JCO 2008

Pavel et al Lancet 2011

Lanreotide + Sunitinib
Sunitinib
Placebo + Octreotide
Everolimus + Octreotide

PFS (E+O) 16.4 mo.
PFS (P+O) 11.4 mo.

HR 0.77 (95% CI 0.59-1.00)
p = 0.026
Bevacizumab vs Interferon-alpha in advanced carcinoid (SWOG 0518)

Phase III Open Labeled

Advanced Carcinoid with poor prognosis:
- Progressive
- Refractory syndrome
- G2 with 6+ lesion

(N=400)

Bevacizumab 15 mg/kg q21 d
Interferon 5 mu 3 d/wk
octreotide LAR 20 mg q21 d

Treatment until disease progression

No significant difference between Interferon and Bevacizumab based on central radiology PFS
Final data not available yet

Primary end point:
- PFS (RECIST)

Secondary end point:
- Tumor response, OS, biomarkers, safety

Multiphasic CT or MRI performed every 9 wk
Systemic chemotherapy
For whom?
Systemic Chemotherapy in intestinal NEN

- **Neuroendocrine Carcinoma G3 (any site)**
  - Cisplatin/Etoposide
  - Carboplatin/Etoposide
  - FOLFOX
  - FOLFIRI

- **Neuroendocrine Tumors G2/ G3 ?**

Chemotherapy in GI NET?

ENETS Consensus Guidelines 2012 do not recommend systemic chemotherapy in intestinal NET*

- Capecitabine (1000 mg/m²) + Bevacizumab (BETTER Study)
  - 47 GI NET: 18% PR, 69% SD; median PFS 23.4 mo.
    
    (Ducreux et al ASCO 2012)

- 5-FU (200 mg/m² tgl.) + Octreotide LAR (20 mg/mo.)
  - 29 NET: 24% PR, 69% SD
    
    (Brizzi et al, BMC Cancer 2009)

- Temozolomide (100mg/d) + Bevacizumab + Octreotide LAR
  - 15 GEP NET: 57% PR, 1% CR, 21% SD, 14% PD
    
    (Koumarianou et al, ERC 2012)

*unless high grade/ higher G2 NET
Management of metastatic non-resectable intestinal NET

Modified ENETS Consensus Guidelines 2012

Functional NET
1. SSA
2. IFN-α

Loco-regional Tx
Debulking; RFA

NET G1/G2
G1/ G2 -10% Ki67 Low/higher tumor burden; +/- PD

Non-functional NET

SSA
PD
IFN-α
PD
PRRT
RADIANT-4

G1/ G2
High tumor burden if SRS positive

G1/ G2 if SRS negative
?

NEC G3

Cisplatin + Etoposide

G1/G2 - 10% Ki67
Low/higher tumor burden; +/- PD

IFN-α CTX (G2)

Everolimus

## Clinical Trials in Midgut NET (Carcinoids)

<table>
<thead>
<tr>
<th>Study Regimen</th>
<th>NCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Telotristat Etiprate</strong> (LX1606) in Patients with SSA refractory Carcinoid Syndrome (TELESTAR)</td>
<td>NCT01677910</td>
</tr>
<tr>
<td><strong>177Lu-DOTATATE PRRT vs. high dose octreotide</strong> (NETTER-1) in midgut NET</td>
<td>NCT01578239</td>
</tr>
<tr>
<td><strong>Sunitinib + Lanreotide</strong> vs. Placebo + Lanreotide in midgut NET (SUNLAND)</td>
<td>NCT01731925</td>
</tr>
<tr>
<td><strong>Pazopanib vs Placebo</strong> in progressive NET</td>
<td>NCT01841736</td>
</tr>
<tr>
<td><strong>Axitinib + Octreotide LAR</strong> vs. Placebo + Octreotide LAR in non-pancreatic NET</td>
<td>NCT01744249</td>
</tr>
<tr>
<td><strong>Bevacizumab + Octreotide LAR vs. Interferon + Octreotide LAR</strong> (SWOG 0518)*</td>
<td>NCT00569127</td>
</tr>
<tr>
<td><strong>Everolimus + BSC vs. Placebo + BSC in advanced GI or Lung NET</strong> (RADIANT-4)*</td>
<td>NCT01524783</td>
</tr>
</tbody>
</table>

* Enrollment completed
Thank you!