UPDATE IN THE MANAGEMENT OF NEUROENDOCRINE TUMOURS

Please see Brief Summary and accompanying full Prescribing Information on slides 29-32.
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NEUROENDOCRINE TUMOUR (NET) OVERVIEW
NEUROENDOCRINE TUMOURS (NETs)

SITE OF PRIMARY TUMOUR

(Incidence per 100,000)*

- Arise from cells of the neuroendocrine system
- Most common type are gastroenteropancreatic NETs (GEP-NETs) of the gastrointestinal (GI) system
- Generally small (< 1 cm in diameter) and slow-growing
- Have metastatic potential

**GI SYSTEM (2.89)**

- Pancreas (0.32)
- Liver (0.04)
- Stomach (0.30)
- Duodenum (0.19)
- Jejunum/ileum (0.67)
- Cecum (0.16)
- Appendix (0.15)
- Colon (0.20)
- Rectum (0.86)

**LUNG (1.35)**

**THYMUS (0.02)**

**OTHER/UNKNOWN (0.74)**

*Age-adjusted annual incidence per 100,000 in the 2000 US population; from the SEER 17 registry

NETs ARE MORE PREVALENT THAN MANY TUMOURS OF THE GI SYSTEM

A LACK OF DISTINCT SYMPTOMS MAY DELAY NET DIAGNOSIS

NETs ARE TYPICALLY PRESENT FOR 5-7 YEARS PRIOR TO DIAGNOSIS

ASYMPTOMATIC NETs

- Also called nonfunctioning NETs
- More common than symptomatic NETs
- Do not cause clinical syndromes
- Usually present due to mass effects and/or metastatic disease

SYMPTOMATIC NETs

- Also called functioning NETs
- Release bioactive substances to the bloodstream
- May cause paraneoplastic disease
- Symptoms may mimic other conditions

(e.g. symptomatic GEP-NETs typically produce flushing and diarrhoea)

NEARLY HALF OF ALL NETs ARE ADVANCED AT DIAGNOSIS

*Includes the 78.4% of NET patients in the SEER 17 registry with staging information available at diagnosis.

ADVANCED DISEASE IS ASSOCIATED WITH POORER 5-YEAR SURVIVAL

- Localised: 79%
- Regional Spread: 65%
- Distant Metastasis: 27%

WITHOUT TREATMENT, THE MAJORITY OF PATIENTS WITH ADVANCED MIDGUT NETs WILL PROGRESS WITHIN 1 YEAR

The majority of NETs express somatostatin receptors (SSTRs).

Approximately 80% of GEP-NETs express the SSTR2 subtype.

**POTENTIAL THERAPEUTIC TARGET:** SOMATOSTATIN SIGNALLING IN NETs

- Somatostatin signalling:
  - Decreases hormone secretion and controls symptoms
  - Promotes cell death (apoptosis)
  - Inhibits cell growth
- The majority of NETs express somatostatin receptors (SSTRs)
- Approximately 80% of GEP-NETs express the SSTR2 subtype

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DIRECT AND INDIRECT ANTIPROLIFERATIVE EFFECTS OF SOMATOSTATIN SIGNALLING

SOMATOSTATIN RECEPTOR ACTIVATION

Binding of somatostatin receptors on tumour cells

- Inhibition of growth factor effects
- Pro-apoptotic effect

Direct antiproliferative effect

- Inhibition of cell cycle

Indirect antiproliferative effect

- Inhibition of growth factor and trophic hormones
- Inhibition of angiogenesis
- Immune system modulation

Systemic effect

DELAYING THE PROGRESSION OF NEUROENDOCRINE TUMOURS
PROMID: PIVOTAL PHASE III TRIAL DEMONSTRATING TUMOUR CONTROL BY SANDOSTATIN LAR

• **PROMID**: Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors

• Phase III, randomised, double-blind, placebo-controlled trial

• Designed to evaluate the antiproliferative effects of the somatostatin analogue Sandostatin® (octreotide) LAR® 30 mg

• Conducted at 18 centres in Germany (2001-2008)
PROMID DESIGN AND ENDPOINTS

Randomised Patients (N = 85)
• Treatment naïve
• Karnofsky status > 60%
• Tumour criteria
  - Midgut origin
  - Well-differentiated histology
  - Locally inoperable or metastatic
  - Measurable (CT/MRI)
• Symptomatic or asymptomatic

Primary Endpoint
- TTP (defined as time to tumour progression or time to tumour-related death)

Secondary Endpoints
- Survival time
- Quality of life
- Clinical and biochemical response (in patients with symptomatic disease)
- Safety

# PROMID PATIENT CHARACTERISTICS AT BASELINE

<table>
<thead>
<tr>
<th></th>
<th>Sandostatin LAR 30 mg (N = 42)</th>
<th>Placebo (N = 43)</th>
<th>Total (N = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>63.5 (38-79)</td>
<td>61 (39-82)</td>
<td>62 (38-82)</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>20 (47.6)</td>
<td>23 (53.5)</td>
<td>43 (50.6)</td>
</tr>
<tr>
<td><strong>Months since diagnosis (range)</strong></td>
<td>7.5 (0.8-271.7)</td>
<td>3.3 (0.8-109.4)</td>
<td>4.3 (0.8-271.7)</td>
</tr>
<tr>
<td><strong>Karnofsky performance status &gt; 80% (%)</strong></td>
<td>35 (83.3)</td>
<td>38 (88.4)</td>
<td>73 (85.9)</td>
</tr>
<tr>
<td><strong>Symptomatic disease (%)</strong></td>
<td>17 (40.5)</td>
<td>16 (37.2)</td>
<td>33 (38.8)</td>
</tr>
<tr>
<td><strong>Resection of primary tumour (%)</strong></td>
<td>29 (69.1)</td>
<td>27 (62.8)</td>
<td>56 (65.9)</td>
</tr>
<tr>
<td><strong>Ki-67 up to 2% (%)</strong></td>
<td>41 (97.6)</td>
<td>40 (93.0)</td>
<td>81 (95.3)</td>
</tr>
<tr>
<td><strong>Octreoscan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (%)</td>
<td>32 (76.2)</td>
<td>31 (72.1)</td>
<td>63 (74.1)</td>
</tr>
<tr>
<td></td>
<td>4 (9.5)</td>
<td>6 (14.0)</td>
<td>10 (11.8)</td>
</tr>
<tr>
<td><strong>Liver involvement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 10% (%)</td>
<td>32 (76.2)</td>
<td>32 (74.4)</td>
<td>64 (75.3)</td>
</tr>
<tr>
<td>&gt; 10% (%)</td>
<td>10 (23.8)</td>
<td>11 (25.6)</td>
<td>21 (24.7)</td>
</tr>
<tr>
<td><strong>Chromogranin A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated (%)</td>
<td>26 (61.9)</td>
<td>30 (69.8)</td>
<td>56 (65.9)</td>
</tr>
<tr>
<td>Not elevated (%)</td>
<td>15 (35.7)</td>
<td>12 (27.9)</td>
<td>27 (31.8)</td>
</tr>
</tbody>
</table>

SANDOSTATIN LAR 30 MG SIGNIFICANTLY PROLONGS TTP* OVER PLACEBO

Results seen in the Sandostatin LAR 30 mg group, compared with placebo

- More than double the median TTP (14.3 months with Sandostatin LAR 30 mg vs 6.0 months with placebo; \( P = 0.000072 \))
- 66% reduction in the risk of disease progression (HR = 0.34)

*TTP: Time to tumour progression or tumour-related death
THE MAJORITY OF PATIENTS IN THE PROMID TRIAL WERE ASYMPTOMATIC

Sandostatin LAR 30 mg prolonged TTP over placebo, regardless of symptomatic or asymptomatic disease

- Symptomatic: HR = 0.23 (95% CI: 0.09-0.57)
- Asymptomatic: HR = 0.25 (95% CI: 0.10-0.59)

MAJORITY OF PATIENTS WHO RECEIVED SANDOSTATIN LAR 30 MG ACHIEVED STABLE DISEASE AT 6 MONTHS*

P = 0.0079

*As defined by WHO criteria
SANDOSTATIN LAR IS GENERALLY WELL TOLERATED\(^1\)

OBSERVED SAFETY FINDINGS IN THE PROMID TRIAL WERE CONSISTENT WITH THOSE SEEN IN PREVIOUS STUDIES OF SANDOSTATIN LAR IN PATIENTS WITH NETs\(^1-3\)

<table>
<thead>
<tr>
<th>Adverse events in PROMID(^3)</th>
<th>Sandostatin LAR 30 mg (N = 42)</th>
<th>Placebo (N = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Most frequent serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Haematopoietic system</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>General health status (fatigue, fever)</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Adverse event causing discontinuation</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

GUIDELINES

CPO: Please provide your local guidelines here
Diarrhoea and flushing are the two most common GEP-NET symptoms.¹
- Patients may have up to 30 stools per day, accompanied by pain.²
- Flushing is an outwardly visible sign of the disease.²

Potentially life-threatening dehydration, hypotension, arrhythmias, and unconsciousness can develop from early symptoms, like diarrhoea and flushing.³

References:
IN FUNCTIONAL CARCINOID PATIENTS:
REDUCTION IN THE FREQUENCY OF DIARRHOEA
WITH SANDOSTATIN LAR 20 MG

Median Number of Daily Episodes

Baseline: 4.0
24 Weeks: 2.1

N = 20

Data on file. Novartis Pharma AG.
IN FUNCTIONAL CARCINOID PATIENTS:
REDUCTION IN THE FREQUENCY OF FLUSHING EPISODES
WITH SANDOSTATIN LAR 20 MG

Median Number of Daily Episodes

Baseline: 5.9
24 Weeks: 0.6
N = 20

90% REDUCTION
IN FUNCTIONAL CARCINOID PATIENTS:

SUPPRESSION OF 5-HIAA* LEVELS
WITH SANDOSTATIN LAR 20 MG

*5-hydroxyindoleacetic acid: serotonin metabolite used to assess tumour hormone secretion
** 20 and/or 24 weeks
SANDOSTATIN LAR DOSING

SANDOSTATIN IS AVAILABLE IN A SUBCUTANEOUS (SC) FORMULATION FOR BREAKTHROUGH SYMPTOMS

TUMOUR CONTROL

• Sandostatin LAR 30 mg IM every 4 weeks
• Continue treatment in the absence of tumour progression

SYMPTOM CONTROL

IN PATIENTS WITH ADEQUATE SYMPTOM CONTROL WITH SANDOSTATIN SC

• Initiate Sandostatin LAR 20 mg every 4 weeks
• Continue Sandostatin SC for 2 weeks after initiating Sandostatin LAR
• After 3 months, assess need for dose adjustments based on symptomatic response
SUMMARY

- NETs are more prevalent than many other tumours of the GI system.\(^1,2\)
- Although most NETs are small tumours, they can progress to metastatic disease, which has implications for survival.\(^2,3\)
- Nearly half of all NET patients are diagnosed with advanced disease.\(^2\)
- The randomised, placebo-controlled phase III PROMID trial demonstrated that:
  - Sandostatin LAR 30 mg is the only somatostatin analogue to significantly prolong TTP in patients with advanced midgut NETs.\(^4,5\)
  - Significantly more patients achieved stable disease with Sandostatin LAR than with placebo.\(^4\)
- Sandostatin LAR is the first and only somatostatin analogue proven to have an antiproliferative effect on advanced midgut NETs.\(^5\)
- Updated treatment guidelines now recommend Sandostatin LAR for early tumour control in patients with advanced midgut NETs or unknown primary tumour location.\(^6\)

• The most common symptoms are diarrhoea and flushing.  

• Potentially life-threatening dehydration, hypotension, arrhythmias, and unconsciousness can develop from early symptoms, like diarrhoea and flushing.

• In functional carcinoid patients, Sandostatin LAR has been proven to reduce:
  – The frequency of diarrhoea and flushing episodes.
  – 5-HIAA levels.

• Sandostatin is available in a subcutaneous (SC) formulation for breakthrough symptoms.

FULL PRESCRIBING INFORMATION

CPO: Please provide your local full Prescribing Information
Important note: Before prescribing, consult full prescribing information.

Presentation: Octreotide acetate. Vials containing 10 mg, 20 mg or 30 mg octreotide free peptide supplied as powder (microspheres) for suspension for injection together with a prefilled syringe (solvent for parenteral use), containing: sodium carboxymethylcellulose 12.5 mg, mannitol 15 mg; water for injection qs ad 2.5 mL; two needles [40 mm (1.5 inch), 19 gauge]. Sandostatin® LAR® suspension contains less than 1 mmol (23 mg) of sodium per dose, i.e. essentially ‘sodium-free’.

Indication: Acromegaly: in patients who are adequately controlled on SC treatment with Sandostatin; in patients in whom surgery or radiotherapy is inappropriate or ineffective; in the interim period until radiotherapy becomes fully effective. Relief of symptoms associated with functional gastro-entero-pancreatic endocrine tumours: carcinoid tumours with features of the carcinoid syndrome, VIPomas, glucagonomas, gastrinomas/Zollinger-Ellison syndrome, insulinomas, GRFomas. Treatment of patients with advanced neuroendocrine tumours of the midgut or unknown primary tumour location.

Dosage: 10 to 30 mg every 4 weeks, administered as a deep intragluteal injection.
Contraindications: Known hypersensitivity to octreotide or to any of the excipients.

Warnings/Precautions: Dose adjustments of drugs such as beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary; caution in patients with insulinomas; diabetes mellitus thyroid function should be monitored in patients receiving prolonged treatment with octreotide. Periodic examination of gallbladder; monitoring of vitamin B12 levels in patients who have a history of vitamin B12 deprivation; caution in patients with pregnancy, patients should be advised to use adequate contraception if necessary. Patients should not breast-feed during Sandostatin LAR treatment.

Interactions: Impaired intestinal absorption of ciclosporin, cimetidine; increased bioavailability of bromocriptine. Caution with concomitant use of drugs mainly metabolised by CYP3A4 and which have a low therapeutic index.
**BRIEF SUMMARY (CONTINUED)**

**Adverse reactions:** Very common (≥1/10) adverse drug reactions are: diarrhoea, abdominal pain, nausea, constipation, flatulence, headache, cholelithiasis, hyperglycaemia, and injection-site localised pain. Common (≥1/100, <1/10) adverse drug reactions are: dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools, discolouration of faeces, dizziness, hypothyroidism, thyroid dysfunction (e.g. decreased thyroid stimulating hormone [TSH], decreased Total T4, and decreased Free T4), cholecystitis, biliary sludge, hyperbilirubinaemia, hypoglycaemia, impairment of glucose tolerance, anorexia, elevated transaminase levels, pruritus, rash, alopecia, dyspnoea, and bradycardia. Uncommon (≥1/1000, <1/100) adverse drug reactions are: dehydration, and tachycardia. Post-marketing the following adverse reactions have been reported: anaphylaxis, allergy/hypersensitivity reactions, urticaria, acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice, arrhythmia, increased alkaline phosphatase levels, and increased gamma glutamyl transferase levels.

**Packs and prices:** Country specific.

**Legal classification:** Country specific.