**Neuroendocrine Tumour of the Colon or Rectum**

Primary Tumour (T)
Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
T1: Tumour invades lamina propria or submucosa and size 2 cm or less
T1a: Tumour size less than 1 cm in greatest dimension
T1b: Tumour size 1-2 cm in greatest dimension
T2: Tumour invades muscularis propria or size greater than 2 cm with invasion of lamina propria or submucosa
T3: Tumour invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
T4: Tumour invades peritoneum or other organs
For any T, add (m) for multiple tumours

Regional Lymph Nodes (N)
Nx: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastases

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

**Neuroendocrine Tumour of the Pancreas**

Primary Tumour (T)
Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
Tis: Carcinoma in situ
T1: Tumour limited to the pancreas, 2 cm or less in greatest dimension
T2: Tumour limited to the pancreas, more than 2 cm in greatest dimension
T3: Tumour extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4: Tumour involves the celiac axis or the superior mesenteric artery (unresectable primary tumour)

Regional Lymph Nodes (N)
Nx: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastases

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

### Appendiceal Carcinoid Tumour

Primary Tumour (T)
Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
T1: Tumour 2 cm or less in greatest dimension
  T1a: Tumour 1 cm or less in greatest dimension
  T1b: Tumour more than 1 cm but not more than 2 cm
T2: Tumour more than 2 cm but not more than 4 cm or with extension to the cecum
T3: Tumour more than 4 cm or with extension to the ileum
T4: Tumour directly invades other adjacent organs or structures, e.g., abdominal wall and skeletal muscle

Regional Lymph Nodes (N)
Nx: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastases

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

### Neuroendocrine Tumour of the Adrenal Gland

Primary Tumour (T)
Tx: primary tumour cannot be assessed
T0: No evidence of primary tumour
T1: Tumour 5 cm or less in greatest dimension, no extra-adrenal invasion
T2: Tumour greater than 5 cm, no extra-adrenal invasion
T3: Tumour of any size with local invasion, but not invading adjacent organs
T4: Tumour of any size with invasion of adjacent organs

Regional Lymph Nodes (N)
Nx: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastases

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

## APPENDIX B: EVIDENCE TABLES

**Table 1:** Clinical studies

| *Author (trial)* | *Design* | *Treatments* | *Patients (n)* | *Response* | *Survival* | *Adverse events* |
|---|---|---|---|---|---|---|
| **OCTREOTIDE** | | | | | | |
| Li J. [27]<br>2014<br>ASCO abstract<br>**(NCT01480986)** | phase II | IP regimen: irinotacen 180 mg/m$^2$ on d1, and cisplatin 50 mg/m$^2$ on d1, q 2 wks for 6 cycles (n=40)<br><br>After chemotherapy, pts without disease progression received Ooctreotide LAR (n=13 of 27 pts confirmed without progression) | NET (n=40) | | PFS (med after chemotherapy): 3.1 mo octerotide LAR vs 4.1 mo no octreotide LAR, p=0.908 | Gr 3-4 for entire regimen:<br>neutropenia: 50%<br>leukopenia: 35%<br>nausea/vomiting: 7.5%<br>diarrhea: 5%<br>anorexia: 5% |
| Bajetta E.<br>2013 [28]<br>ASCO abstract<br>**(I.T.M.O)** | phase II | octreotide LAR (30 mg q 28 d) + everolimus (10 mg/d) | advanced well differentiated gastroenteropancreatic-NET (n=50)<br><br>primary (%)<br>**pancreas 28%**<br>**unknown 28%**<br>lung 22%<br>ileum 18%<br>jejunum + duodenum 4% | ORR: 20%<br>CR: 4% (n=2)<br>PR: 16% (n=8)<br>SD: 72% (n=36)<br>Clinical benefit (CR+PR+SD): 92% | TTP(med): 16.3 mo | Gr 3<br>skin rash: 1 pt<br>stomatitis: 8% (n=4)<br>diarrhea: 22% (n=11)<br><br>Gr 4:<br>mucositis:1 pt |
| Wolin EW.[29]<br>2013<br>**(NCT00690430)** | phase III | 1.P arm: pasireotide LAR (60 mg IM q 28 d)<br><br>2. O arm: octreotide LAR (40 mg IM q 28 d) | NET (n=110)<br><br>primary (%)<br>**sm intestine 72% P arm vs. 81% O arm** | Symptom response (6-mo): 21% (n=9/43) P arm vs. 27% (n=12/45) O arm, OR: 0.73 (95% CI 0.27-1.97; p=0.53) | PFS (med): 11.8 mo P arm vs. 6.8 mo O arm (HR=0.46; p=0.045) | Gr 3-4 (P vs. O arms):<br>hyperglycemia: 11% vs. 0%<br>diarrhea: 9% vs. 7%<br>abdominal pain: 2% vs. 9% |
| Pavel ME.<br>2011[30-34]<br>**(RADIANT-2)**<br>(Lancet article + ASCO abstracts) | phase III RCT | 1. EO: everolimus (10 mg/d PO) + octreotide LAR (30 mg IM q 4 wks)<br><br>2. PO: placebo + octreotide LAR (30 mg IM q 4 wks) | NET, advanced low-to-intermed grade w/ radiologic progression in the past 12 mo (n=429)<br><br>primary (%)<br>**sm intestine 52%**<br>lung 10%<br>colon 6.5%<br>pancreas 6% | CgA response: overall 46% EO vs. 29% PO<br><br>5-HIAA response: overall 61% EO vs. 47% PO | PFS (med):<br>16.4 mo EO vs. 11.3 mo PO (HR progress/death: 0.77; 95% CI 0.59-1.00; p=0.026)<br><br>*Subgroup: disease site (n=307)*<br>sm int PFS (med): ↑ 4.6 mo<br>lung PFS (med): ↑ 8.0 mo<br>colorec PFS (med): ↑ 23.3 m<br><br>*Prog factors for med PFS:* | stomatitis: 62% EO vs. 14% PO<br><br>rash: 37% EO vs. 12% PO<br><br>fatigue: 31% EO vs. 23% PO<br><br>diarrhoea: 27% EO vs. 16% PO |

| *Author (trial)* | *Design* | *Treatments* | *Patients (n)* | *Response* | *Survival* | *Adverse events* |
|---|---|---|---|---|---|---|
| | | | liver 4%<br>other 2.1%<br>missing 0.25% | | chromogranin A (HR 0.47; 95% CI 0.34-0.65; p<0.001)<br>WHO PS (HR 0.69; 95% CI 0.52-0.90; p=0.006)<br>bone involvement (HR 1.52; 95% CI 1.06-2.18; p=0.02)<br>lung primary site (HR 1.55; 95% CI 1.01-2.36; p=0.04)<br><br>Adjusted HR progression/death: 0.62; 95% CI 0.51-0.87; p=0.003 | |
| Rinke A. 2009[7,35] **(PROMID)** (JCO article + ASCO abstract) | phase III RCT | 1. octreotide LAR (30 mg IM monthly)<br>2. placebo | well-differentiated NET (n=85)<br><br>primary site **midgut or unknown primary believed to be of midgut** if a primary within pancreas, chest, elsewhere was excluded; tx-naïve | SD (6-mo): 66.7% octreo vs. 37.2% placebo | PFS (med): 14.3 mo octreo vs. 6 mo placebo (HR 0.34; p<0.0001)<br><br>Deaths: 7 octreo vs. 9 placebo<br>OS (med): could not be estimated due to low # deaths (HR 0.81; 95% CI 0.30-2.18) | Most frequent severe: hematopoietic system (octreotide 5 pts vs. placebo 1 patient)<br><br>fatigue and fever (octreotide 8 pts vs. placebo 2 pts)<br><br>WHO Gr 2-4: more often in the octreotide arm (diarrhea, flatulence) |
| Arnold R. 2005[36] (abstract) | phase III | 1. octreotide + IFN-alpha<br>2. octreotide alone | progressive metastatic NET (n=125)<br><br>primary site **foregut (mainly pancreatic) and the midgut** | PR (12-mo): 5.7%<br>SD (12-mo): 15.2%<br>(no diff b/t arms) | OS (med); 54 mo O+IFN vs. 32 mo O alone | |
| Yao JC. 2008[37] **(RADIANT-1)** | phase II | 1. everolimus (5 mg/d) + octreotide LAR (30 mg q 4 wks)<br>2. everolimus (10 mg/d) + octreotide LAR (30 mg q 4 wks) | NET, advanced low-intermed Gr (n=60)<br><br>primary site (%)<br>**pancreas 48%**<br>**sm intestine 27%**<br>lung 7%<br>gastric 2%<br>thymus 2%<br>rectum 5%<br>renal 2%<br>unknown 8% | whole group:<br>PR: 22% (n=13)<br><br>SD: 70% (n=42) | PFS whole group (med): 13.8 m<br><br>OS (med): not reached<br>OS (1-yr): 83%; (2-yr): 81%<br><br>*Subgroup (SD vs. progressive)*<br>PFS (med): 17 mo SD vs. 11.5 mo progressive disease; p<0.01 | most common:<br><br>mild aphthous ulceration<br><br>Gr 3-4 (≥10% pts):<br><br>diarrhea, 11%<br><br>fatigue, 11%<br><br>hypophosphatemia, 11% |

| *Author (trial)* | *Design* | *Treatments* | *Patients (n)* | *Response* | *Survival* | *Adverse events* |
|---|---|---|---|---|---|---|
| Savelli G. 2012[38] | phase IIa | (90)Y-DOTATOC | advanced stage well differentiated **gastro-entero-**PNET (n=38)<br><br>primary site (%)<br>**pancreas 17%**<br>**ileum 5%**<br>**duodenum 1%**<br>**rectum 1%**<br>renal 2%<br>breast 1%<br>unknown 13% | PR: 43.6%<br>SD: 25.6% | PFS (med): 22.3 mo | main toxicity:<br>renal (3 pts with chronic renal failure)<br><br>mild hematologic toxicity (Gr 1-3) affected most of the patients. |
| Imhof A. 2011[39] | phase II open label | [(90)Y-DOTA]-TOC octreotide (3.7 GBq/m$^2$ per injection; 1 injection per cycle) | advanced/ meta-static (n=1109)<br><br>primary site (%)<br>*carcinoid 43%*<br>**sm intestine 56%**<br>bronchus 18%<br>lg intestine 9%<br>upper gut 1.5%<br>other 2.5%<br>unknown 14%<br><br>*PNET 31%*<br><br>*rare NET 9.3%*<br><br>*unknown 16.7%* | *Morphologic* 34.1% (n=378)<br><br>*Biochemical* 15.5% (n=172)<br><br>*Clinical* 29.7% (n=329) | OS (23-mo): 54.9%<br><br>Median OS: 94.6 mo<br><br>OS predictors:<br>age, previous surgery, previous chemo, Liver mets, bone mets, and response | Gr 3-4 hematologic: 12.8% (142)<br><br>Gr 4-5 renal (permanent): 9.2% (103) |
| Claringbold PG. 2011[40] | phase II | capecitabine (1,650 mg/m$^2$/d for 14 days + (177)Lu-octreotate (7.8 GBq 8-weekly) x 4 cycles<br>* 2.4 Gy per cycle to kidneys;<br>4.8 Gy per cycle to liver | disseminated, progressive, unresectable NET (n=33)<br><br>primary site (%)<br>**sm intestine 39%**<br>unknown 18%<br>pancreas 9%<br>lung 6%<br>colon 6%<br>other 21% | CR: 0%<br>PR: 24%<br>SD: 70% | PFS (med): not reached, 16 mo<br>OS (med): not reached, 16 mo<br><br>OS (1-yr): 91% (75-98%)<br>OS (2-yr): 88% (71-96%) | Gr 3 thrombocytopenia: 1 pt<br><br>nephrotoxicity: none |
| Brizzi MP. 2009[15] | phase II | 5FU (200 mg/m2 IV daily) + LAR octreotide (20 mg | advanced/ meta-static well-diff NET (n=29) | PR: 24.1% (n=7)<br>SD: 69.0% (n=20) | PFS (med): 22.6 mo<br>OS (med): not reached | diarrhea 65.4%<br><br>hand-foot syndrome 34.5% |

| *Author (trial)* | *Design* | *Treatments* | *Patients (n)* | *Response* | *Survival* | *Adverse events* |
|---|---|---|---|---|---|---|
| | | monthly) | primary site (%)<br>**pancreas 45%**<br>functioning 17%<br>unknown 24%<br>sm intestine 24%<br>appendix 3%<br>colon 3% | *Biochemical (chromogranin A):*<br>48.0% (n=12) | Symptom relief: 60% (9/15 pts) | asthenia 37.9%<br><br>nausea-vomiting 27.9% |
| Seregni E. 2010[41] | phase II | [(177)Lu]DOTA-TATE (5.55 GBq) and [(90)Y]DOTA-TATE (2.6 GBq) alternating x 4 cycles | refractory NET (n=26)<br><br>primary site (%)<br>**intestine 38.5%**<br>pancreas 23%<br>other 19%<br>unknown 11.5% | PR: 67% (n=10) at 3-mos post | n/a | leukocytopenia Gr 1-2: 2 pts<br><br>thrombocytopenia Gr 1: 1 pt<br><br>well tolerated; no organ damage |
| Cwikla JB. 2010[42] | phase II | [(90)Y]DOTA-TATE | progressive **gastroentero-PNET** (n=56)<br><br>primary site (%)<br>**foregut 42%**<br>**midgut 48%**<br>unknown 10% | *Radiologic*<br>PR: 23% (n=13)<br>SD: 77% (n=43)<br>*Clinical*<br>PR: 72% (n=43)<br>SD: 16% (n=9) | PFS (med): 17 mo (4.5 mo in early PD; 19.5 mo in PR / SD)<br><br>OS (med): 22 mo (9.5 mo in early PD; 23.5 mo in PR / SD) | Gr 2-3 renal toxicity: 5 patients<br><br>Gr 3-4 hematological toxicity: 10% during therapy (persisted in 5%) |
| Waldherr C. 2001[43] | phase II | [(90)Y-DOTA]-TOC (6000 MBq/m2 x 4 injections) q 6 wks | **gastroentero-pancreatic NET** (n=41)<br><br>primary site (%)<br>EPT 34%<br>intestinal 19.5%<br>bronchial 17%<br>unknown 19.5%<br>other 10% | Overall: 36% for endocrine NET<br><br>CR: 2% (1 pt)<br>PR: 22% (n=9) | OS (2-yr): 76%<br><br>Reduction of symptoms: 83%<br>Reduction in pain: 100% of those w/morphine-depend pain | Gr 3 pancytopenia: 5%<br><br>vomiting after injection: 23%<br><br>Gr 3-4 renal toxicity: none |
| **LANREOTIDE** | | | | | | |
| Caplin, M.E. [6] 2014 **(CLARINET)** | phase III RCT | 1) extended-release aqueous-gel formulation of lanreotide (120 mg) q 28 days for 96 wks (n=101) | advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor–positive NET (n=204) | CgA reduction ≥50%: 42% (n= 27/64) lanreotide vs. 5% (n=3/64) placebo, p<0.001 | PFS (med): not reached lanreotide vs. 18.0 mo placebo, p<0.001<br><br>HR for progression or death, 0.47; 95% CI 0.30-0.73 | most common:<br>diarrhea: 26% lanreotide and 9% placebo<br><br>7 serious events (hyperglycemia, diabetes mellitus, nausea, vomiting, abdominal pain, biliary fistula, and |

| *Author (trial)* | *Design* | *Treatments* | *Patients (n)* | *Response* | *Survival* | *Adverse events* |
|---|---|---|---|---|---|---|
| | | 2) placebo q 28 days for 96 wks (n= 103) | <u>primary site</u> (%)<br>lancreotide vs. placebo<br>**pancreas 42% vs. 48%**<br>midgut 33% vs. 39%<br>hindgut 11% vs. 3%<br>unknown/other 15% vs.11% | | PFS (24 mo): 65.1% (95% CI 54.0-74.1) lanreotide vs. 33.0% (95% CI 23.0-43.3) placebo | cholelithiasis) in the lanreotide group and one event (bile duct stenosis) in the placebo group |
| Martin-Richard M.[44]<br>2013<br>**(NCT00326469)** | phase II | lanreotide autogel, 120 mg q 28 days over 12 mo | progressive NET (n=30)<br><br><u>Primary tumour</u><br>**midgut 40%**<br>pancreatic 27% | SD: 89% (n=24)<br>PR: 4% (n=1)<br><br>CgA normalised/ decreased by ≥30% at 8 wks: 70% | PFS (med): 12.9 mo (95% CI 7.9-16.5) | most common:<br>diarrhea: 40%<br>asthenia: 20%<br>flatulence: 10%<br>injection- site pain: 10%<br><br>1 pt had severe event (aerophagia) and 1 pt had a serious event (acute renal failure) |

*Abbreviations: ASCO = American Society of Clinical Oncology: CI = confidence interval; CR = complete response; Gr = grade; HR = hazard ratio; mo = months; NET = neuroendocrine tumour; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; pt = patient; SD = stable disease; TTP = time to progression*