Management of lung carcinoid tumors: systemic treatment

Baudin E for the GR-NET team
### WHO 2004 classification of lung NETs

<table>
<thead>
<tr>
<th>Architecture</th>
<th>Mitoses/2 mm²</th>
<th>Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical</td>
<td>Endocrinoid</td>
<td>0-1 AND Absence</td>
</tr>
<tr>
<td>Atypical</td>
<td>Endocrinoid</td>
<td>2-10 OR Rare, focal</td>
</tr>
<tr>
<td>Poorly</td>
<td>Solid</td>
<td>&gt;10 Frequent</td>
</tr>
</tbody>
</table>

Ki-67 immunostaining not included

Malignancy compatible with all categories
Epidemiology of lung neuroendocrine tumors (Travis, London Dec 2007)

- Typical C: 2%
- Atypical C: 0.2%
- Large Cell EC: 3%
- Small Cell EC: <20%
- Others: >75%
Lung carcinoid treatment: background

- No prospective study
- Mostly retrospective studies that analyzed bronchial NET mixed with other primary sites,
- A few prospective trials
- Low level of evidence
- Expert consensus guidelines and recommendations
  - NANETS 2010
  - ESMO and NCCN 2013
  - ENETS 2014
Characterization of lung carcinoid prior treatment

- Age, gender, comorbidity
- WHO 2004
- pTNM UICC 201, liver/bone as the main metastatic sites
- Functioning NET
- Chromogranin A, glucose, calcium
- Multiple endocrine neoplasia type 1
- Somatostatin receptor scintigraphy / FDG PET

Standardization according to WHO, ENET, NANET, UICC
Treat functioning syndrome, first!

Minimum biological work-up: Chromogranin A + Calcium + glucose + additional tests (5-HTAA, ACTH, GHRH...)

Courtesy of Lisa Bodei and Jacques Young.
ENETS recommendations for the control of hormone-related symptoms

Hormone-related symptoms

- Carcinoid Sd (Acromegaly)
- Somatostatin Analogues
- Cushing Sd
- Control of cortisol secretion

- LRT, PRRT, IFN + SSA
- Bilateral Adrenalectomy
Prognosis of lung carcinoids: 5-yr survival as a function of pathology and stage

<table>
<thead>
<tr>
<th>WHO classification versus pN</th>
<th>Typical carcinoid</th>
<th>Atypical carcinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>97-100%</td>
<td>83-100%</td>
</tr>
<tr>
<td>N1</td>
<td>75-100%</td>
<td>54-79%</td>
</tr>
<tr>
<td>N2</td>
<td>50%</td>
<td>0-22%</td>
</tr>
</tbody>
</table>

Prognosis of metastatic NETs: 5-yr survival is heterogenous!

A

![Graph showing survival rate (%)](image)

Survival rate (%) vs. Years after diagnosis of metastatic disease

B

![Graph showing survival rate (%)](image)

Survival rate (%) vs. Years after diagnosis of metastatic disease

Durante C et al ERC 2009: Liver met. number, age, positive tumor slope and primary surgery are risk factors
Lung carcinoid: recommendaions for the control of tumor growth
low level of evidence

- Adjuvant setting: ENETS or NANETS guidelines
  - No standard whatever the R status
  - AC with positive lymph nodes, especially if there is a high proliferative index, should be considered for adjuvant therapy and discussed on an individual patient basis (Level of Evidence 4; Grade of recommendation D for ENETS).
  - Trials urgently required, focus on atypical N positive patients (ENETS)

- Palliative setting:
Adjuvant therapy for atypical carcinoid
no strict consensus!
Lung carcinoid: recommendations for the control of tumor growth

- **Adjuvant setting:**
  - No standard whatever the R status
  - Trials urgently required, focus on atypical N positive patients

- **Palliative setting:**
  - No standard
  - Multidisciplinary staff decision
  - Stratification according to the prognosis
  - Trials urgently required
Treatment of metastatic lung NET consider heterogenous prognosis

Carcinoid Bronchial NET

- Good Prognosis
  - Typical Carcinoid
    - No growth with 6-12 months*
  - Poor prognosis
  - Atypical Carcinoid
    - Growth within 6-12 months**

* Include Atypical Carcinoid with low mitotic count ** include some typical carcinoids
Options in advanced Lung Carcinoid good prognosis

Typical Carcinoid
No-slowly progression

Watch and See

Somatostatin Analogues

Locoregional therapy
Watch and see

- Indolent course of subgroup of patients
- Absence of progression at imaging
- Asymptomatic
- No locoregional morbidity expected
- Low-intermediate tumor burden
- Understanding and Compliance
Somatostatin is expressed in lung NET: higher expression in typical carcinoid

Antitumor effect of SMS analogs: lessons from digestive NET

PROMID: Octreotide LAR 30 mg demonstrates antitumor activity in low tumor burden G1 NET

- **Octreotide LAR**: 42 patients / 27 events
  - Median 15.6 months [95% CI: 11.0–29.4]
  - HR = 0.33 [95% CI: 0.19–0.55]
  - *p* = 0.000017

- **Placebo**: 43 patients / 41 events
  - Median 5.9 months [95% CI: 5.5–9.1]

CLARINET: Lanreotide 120 mg demonstrates antitumor activity in slowly progressive NET

- **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]

\[ \text{P-value derived from stratified log-rank test; HR derived from Cox proportional hazard model.} \]

\[ \text{HR, hazard ratio; ITT, intention-to-treat.} \]

Rinke A et al. *J Clin Oncol* 2009

Caplin M et al, ESMO 2013; Phan A et al. NANETS 2013

26-29 March 2014, Geneva, Switzerland
Multiple organ-targeted treatment strategies

Palliative surgical resection
External radiation beam therapy,
Radiofrequency, cryoablation, microwave
Cement injection
Chemo-, radioactive-, liver embolization …

Mutlidisciplinary staff, mortality<3%
Options in advanced Lung Carcinoid
poor prognosis

Atypical Carcinoid / progressive

- SSA-IFN
- Temozolomide
- PRRT
- EVEROLIMUS

ENETS 2013
NANETS 2010: everolimus available in clinical trials
## Temozolomide in bronchial NET

<table>
<thead>
<tr>
<th>Authors</th>
<th>number</th>
<th>TMZ Regimen</th>
<th>Bronchial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekeblad S 2007</td>
<td>13</td>
<td>100-200 mg/m2 5d</td>
<td>31%</td>
</tr>
<tr>
<td>Kulke M 2009</td>
<td>8</td>
<td>Various</td>
<td>13%</td>
</tr>
<tr>
<td>Lindhom ENETS 2011</td>
<td>23</td>
<td>100-200 mg/m2 5d</td>
<td>17%</td>
</tr>
</tbody>
</table>
Grade uptake at SRS

Absence  Uptake<liver  Uptake=liver  Uptake>liver  Uptake = spleen
Peptide receptor radionucleide therapy: results in selected patients with positive SRS

<table>
<thead>
<tr>
<th>Study</th>
<th>PRRT agent</th>
<th>n</th>
<th>OR-CR</th>
<th>PFS Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waldher 2001</td>
<td>[90Y-DOTA, Tyr3] –Octreotide Phase II</td>
<td>41*</td>
<td>24%</td>
<td>&gt;26</td>
</tr>
<tr>
<td>Kwekkeboom 2008</td>
<td>$[^{177}\text{Lu}}$-DOTA,$^3\text{Tyr}$ –Octreotate Compassionate use</td>
<td>310*</td>
<td>30%</td>
<td>40</td>
</tr>
<tr>
<td>Bushnell 2010</td>
<td>[90Y-DOTA, Tyr3] –Octreotide Phase II Multicentric</td>
<td>90*</td>
<td>4%</td>
<td>16.3</td>
</tr>
</tbody>
</table>

* Progressive 83% (W) or 43%(K) or UK (B)
Kasajima A et al ERC 2011:99 NET including 47 FG, increased expression in Foregut or high Ki67 or stage IV
PIK3CA mutations in 13% of Typical carcinoids (75 pts) and 39% of Atypical carcinoids (23 pts)

Capodanno A et al Oncology Reports 2012
RADIANT-2 antitumor effect of everolimus In429 progressive advanced well differentiated "functioning" NET: phase III double blind placebo controlled trial

1. PFS per-central review

![Graph showing PFS per-central review with Everolimus + octreotide LP 16.4 mo. vs Placebo + octreotide LP 11.3 mo.]

HR 0.77 (95% CI 0.59-1.00) p=0.026

Difference in median PFSs: 5.1 months

Pavel M et al. The lancet nov 2011

2. PFS per-local review

![Graph showing PFS per-local review with Everolimus + octreotide LP 12 mo. vs Placebo + octreotide LP 8.6 mo.]

HR 0.78 (95% CI 0.62-0.98) p=0.018

Difference in median PFSs: 3.4 months

Midgut 51% / Foregut 20% / Others 29%
### Analysis by primary tumor site from RADIANT-2 ASCO 2011

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Median PFS E+O</th>
<th>Median PFS P+O</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>16.4 (13.67-21.19)</td>
<td>11.3 (8.44-4.59)</td>
<td>0.77 (0.59-1.00)</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>Small intestine</strong></td>
<td>18.63 (13.60-25.89)</td>
<td>14.03 (9.40-19.84)</td>
<td>0.77 (0.53-1.13)</td>
<td>0.092</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>13.63 (5.55-14.29)</td>
<td>5.59 (2.79-27.76)</td>
<td>0.72 (0.31-1.68)</td>
<td>0.228</td>
</tr>
<tr>
<td><strong>Colorectal</strong></td>
<td>29.90 (5.59-NA)</td>
<td>6.57 (3.02-13.04)</td>
<td>0.34 (0.13-0.89)</td>
<td>0.011</td>
</tr>
</tbody>
</table>
Bronchial carcinoid: recommandations control of tumor growth

- **Adjuvant setting:**
  - No standard whatever the R status
  - Trials urgently required, focus on atypical N positive patients

- **Palliative setting:**
  - No standard
  - Multidisciplinary staff decision
  - Stratification according to the prognosis
  - No definitive place for platine/gemcitabine/taxane-based chemotherapy, antiangiogenic, or EGFR inhibitors
  - Trials urgently required
RADIANT-4 Study: Advanced (unresectable or metastatic) well differentiated non-functioning progressive GI and lung NETs

- **Primary Endpoint**: PFS by central radiological assessment, (local supportive)
  - **HR target value/PFS median**: 0.59/5 to 8.5 months
- **Interim analysis**: 60% of PFS events
- Stratification by tumor site, WHO and prior SSA

**N = 279**

**Randomize**

- **Everolimus 10 mg/day + best supportive care**
  - **n = 186**
- **Placebo + best supportive care**
  - **n = 93**

Cross-over to open-label only after IA and DMC recommendation

ClinicalTrials.gov identifier: NCT01524783

26-29 March 2014, Geneva, Switzerland
LUNA – Study
Advanced (unresectable or metastatic) well-differentiated lung and thymus progressive NET (typical and atypical according to the WHO criteria).

- Primary endpoint: PFS at one year per RECIST
- 108 patients (36 pts/arm)
- Randomization 1:1:1 to the 3 treatment arms

ClinicalTrials.gov Identifier: NCT01563354
Pathways related to lung carcinoid progression.

Swarts D R et al. Carcinogenesis 2013;34:2726-2737
AGENDA

- **Challenge and answers:**
  - Scarcity and heterogeneity
  - Expert multidisciplinary staffs and networks
  - High quality fluid of clinical data and fluid/tumor/tissue specimen

- **Current status**
  - Palliative options at advanced stage
  - Still a few trials dedicated to lung carcinoids

- **Expected**
  - Active preclinical and translational researches to look for new targets and predictors of response in international trials
Progress within NETworks

ENETS, NANETS …