Advanced thoracic NET (carcinoids) : principles and current role of biological therapies

Eric Baudin and David Planchard for the GR-NET Team

Institut Gustave Roussy, Villejuif, France
Pulmonary NETs (Carcinoids-PC): principles and current role of biological therapies?

Eric Baudin and David Planchard for the GR-NET Team

Institut Gustave Roussy, Villejuif, France
Conflict/Link of Interest

- Advisory board and/or honoraria
  - Novartis
  - Ipsen
  - Pfizer
  - Roche
  - Sanofi

- Research support
  - Pfizer
  - Ipsen
  - HRA
  - Roche
  - Novartis
  - AAA
 Trials in NETS
*pulmonary carcinoids - forgotten primary ?*

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Confirmed phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTC</td>
<td>&gt;2</td>
<td>2</td>
<td>None</td>
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<tr>
<td>MPHeo.PGG</td>
<td>2</td>
<td>0</td>
<td>NA</td>
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<tr>
<td>Ileum</td>
<td>&gt;2</td>
<td>6</td>
<td>SSA class</td>
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<tr>
<td>Pancreas</td>
<td>&gt;2</td>
<td>4</td>
<td>None</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
<td>1 ongoing</td>
<td>NA</td>
</tr>
</tbody>
</table>
Lung Malignancies: Different Targets and Strategies

Lung malignancies

NSCLC

ADC

SqCC

NSCLC–NOS

Chemotherapy

Immunotherapy

EGFR

ALK

No actionable alterations

ROS1

BRAF

MET mutation or amplification

RET

EGFR inhibitors

ALK inhibitors

Chemotherapy

ROS1 inhibitors

BRAF inhibitors

MET inhibitors

RET inhibitors

NOS, not otherwise specified; SqCC, squamous cell carcinoma.
Pulmonary Carcinoid (PC) Treatment: history

- **<2016: treatment principles are extrapolated from digestive NETs**
  - Retrospective studies including, 4 dedicated to P carcinoids
  - Prospective Radiant program: antitumor impact everolimus in NET of various origins including PC
  - Luna trial, first dedicated to lung and thymic carcinoid started in Aug 2013

- **≥2016: pulmonary carcinoid-dedicated trials**
  - LUNA trial is presented at ESMO: first phase II trial
  - SPINET trial starts: first phase III trial
  - Immunotherapy and antiangiogenic strategies are explored in PC

Recommendations for Pulmonary Carcinoid Treatment

**Lung carcinoid**
- Typical carcinoid
  - Residual tumor or slowly progressive*
- Atypical carcinoid or actively progressive

  - Surgery if feasible
  - Observation
  - Somatostatin analogs
  - Interferon
  - Everolimus
  - Chemotherapy (e.g. temozolomide)
  - PRRT

**Control of hormone-related symptoms**
- Typical carcinoid
  - Observation
  - Somatostatin analogs
  - Interferon
  - Everolimus
  - Chemotherapy (e.g. temozolomide)
  - PRRT

**Hormone-related symptoms**
- Atypical carcinoid or actively progressive
  - Somatostatin analogs
  - Interferon
  - Everolimus
  - PRRT

**Carcinoid syndrome**
- Somatostatin analogs

**Cushing’s syndrome**
- Control of cortisol secretion e.g. metapyrone

**Bilateral adrenalectomy**

---

ENETS 2015

PRRT, peptide receptor radionuclide therapy.
Treatment of hormone-related symptoms

Chromogranine A + glucose + tests additionnels (5-HIAA, ACTH, GHRH...) + calcium (dépistage MEN1), echocardiographie...

ACTH, adrenocorticotropic hormone; GHRH, growth hormone–releasing hormone; 5-HIAA, 5-hydroxyindoleacetic acid; MEN1, menin 1/multiple endocrine neoplasia 1.
Pulmonary carcinoids express somatostatin receptors
Carcinoid Syndrome Treatment: no specific treatment for PC

- **Lanreotide**
- **Octreotide**

**First-line: symptom control?**

**Need for active antitumor strategy slope? : yes**

- Surgery if stable
- Imaging guided therapy if PD
- PRRT

**No need for active antitumor strategy**

- Telotristat ethyl
- Interferon alpha
- Pasireotide
- SSA high dose

ENETS 2016 interpretation
Recommendations for Pulmonary Carcinoid Treatment

Lung carcinoid

- Typical carcinoid
  - Residual tumor or slowly progressive*

  - Surgery if feasible
  - Observation
  - Somatostatin analogs
  - Image-guided local therapy
  - As per AC for active progressive disease

- Atypical carcinoid or actively progressive

  - Somatostatin analogs
  - Interferon
  - Everolimus
  - Chemotherapy (e.g. temozolomide)
  - PRRT

Control of hormone-related symptoms

Hormone-related symptoms

- Carcinoid syndrome
  - Somatostatin analogs
  - Interferon
  - PRRT

- Cushing’s syndrome
  - Control of cortisol secretion e.g. metapyrone
  - Bilateral adrenalectomy

ENETS 2015

PRRT, peptide receptor radionuclide therapy.

Somatostatin analogues: retrospective analysis

Median PFS = 17.4 months [95% CI = 8.7–26.0]
SPINET trial: first phase III trial in pulmonary Carcinoids

**Screening/Baseline**

**Randomize**

216 Patients

- **Lanreotide Autogel/Depot**
  120 mg deep SC inj every 4 weeks + BSC

  - **Open-label Treatment**
    - Subjects who have not progressed at the time the 175 events cut-off is reached

- **Placebo**
  Deep SC inj every 4 weeks + BSC

  - **Open-label Treatment**
    - Subjects who have not progressed at the time the 175 events cut-off is reached

  - **Follow-up Period**
    - Subjects who experienced disease progression during double-blind phase
    - Subjects who experienced disease progression during open-label treatment
    - Does not request to enter or meet criteria for open-label treatment

  - **Follow-up Period**
    - Subjects who experienced disease progression during open-label treatment
    - Does not request to enter or meet criteria for open-label treatment
The mTOR pathway expression in bronchial NETs is shown in the figure. A higher expression of p-mTOR and p-S6K in carcinoid > NEC in contrast with p-4EBP1 is indicated.
DNA mutations and CNA in pulmonary neuroendocrine tumors

**PI3K/AKT/mTOR mutations:** 11.7% of carcinoids

**RICTOR/PIK3 CNA:** 48% of carcinoids
<table>
<thead>
<tr>
<th>Trial (n. pts)</th>
<th>Design</th>
<th>Slope /Functioning Sd</th>
<th>N (%) of PC</th>
<th>PR</th>
<th>PFS (mo.)</th>
<th>Invest.arm</th>
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</thead>
<tbody>
<tr>
<td>Pavel M, 2012 (60)</td>
<td>RAMSETE Phase II</td>
<td>Progressive-12 non functioning</td>
<td>22 (36%)</td>
<td>&lt;1%</td>
<td>median,6.6</td>
<td></td>
</tr>
<tr>
<td>Pavel M, 2011 (429)</td>
<td>RADIANT 2 Phase III</td>
<td>Progressive functioning</td>
<td>44 (10%)</td>
<td>3%</td>
<td>median,16.4 (+3.4)</td>
<td></td>
</tr>
<tr>
<td>Yao J, 2015 (302)</td>
<td>RADIANT 4 Phase III</td>
<td>Progressive-6 non functioning</td>
<td>90 (30%)</td>
<td>2%</td>
<td>median, 11 (+7.1)</td>
<td></td>
</tr>
<tr>
<td>Ferrola P, 2016 (124)</td>
<td>LUNA Phase II - RM</td>
<td>Progressive-12 functioning</td>
<td>124 (93%)</td>
<td>2%</td>
<td>PFR*-9 mo 33%</td>
<td></td>
</tr>
</tbody>
</table>

Progression free rate
Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N = 302)
• Absence of active or any history of carcinoid syndrome
• Pathologically confirmed advanced disease
• Enrolled within 6 months from radiologic progression

Randomize

Everolimus 10 mg/day
N = 205
Treated until PD, intolerable AE, or consent withdrawal

Placebo
N = 97

Endpoints:
• Primary: PFS (central)
• Key Secondary: OS

Stratified by:
• Prior SSA treatment (yes vs. no)
• Tumor origin (stratum A vs. B)*
• WHO PS (0 vs. 1)

Approximately 176 PFS events needed to detect a HR of 0.59 with 91.3% power at one-sided significance level of 2.5%

*Based on prognostic level, grouped as: Stratum A (better prognosis) - appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. Stratum B (worse prognosis) - lung, stomach, rectum, and colon except caecum. Crossover to open label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.
Primary endpoint: PFS (Central, RECIST)

Kaplan-Meier median progression-free survival
Everolimus 11.0 months (95% CI 9.2–13.3)
Placebo 3.9 months (95% CI 3.6–7.4)
HR 0.48 (95% CI 0.35–0.67)
p<0.00001 by stratified one-sided log-rank test
RADIANT 4: subgroup analysis

A

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Patients (n)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous SSA treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>157</td>
<td>0.52 (0.34–0.81)</td>
</tr>
<tr>
<td>No</td>
<td>145</td>
<td>0.60 (0.30–0.94)</td>
</tr>
<tr>
<td>Tumour origin*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratum A</td>
<td>153</td>
<td>0.63 (0.40–1.02)</td>
</tr>
<tr>
<td>Stratum B</td>
<td>149</td>
<td>0.43 (0.28–0.66)</td>
</tr>
<tr>
<td>WHO performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>216</td>
<td>0.58 (0.41–0.84)</td>
</tr>
<tr>
<td>1</td>
<td>86</td>
<td>0.50 (0.28–0.91)</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Patients (n)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>90</td>
<td>0.50 (0.28–0.88)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>175</td>
<td>0.56 (0.37–0.84)</td>
</tr>
<tr>
<td>Neuroendocrine tumour of unknown primary origin</td>
<td>36</td>
<td>0.60 (0.24–1.51)</td>
</tr>
<tr>
<td>Study</td>
<td>Median PFS central</td>
<td>Everolimus</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>LUNG NET RADIANT 4</td>
<td>9.2 months</td>
<td>Everolimus: 9.2 months</td>
</tr>
<tr>
<td>LUNG NET RADIANT 2</td>
<td>13.6 months</td>
<td>Everolimus+Oc.: 13.6 months</td>
</tr>
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</table>

Best Percentage Change From Baseline in Tumor Response

<table>
<thead>
<tr>
<th></th>
<th>Everolimus n = 63 (%)</th>
<th>Placebo n = 27 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease</td>
<td>57.9</td>
<td>13.0</td>
</tr>
<tr>
<td>Increase</td>
<td>31.6</td>
<td>69.6</td>
</tr>
<tr>
<td>Contradicted</td>
<td>10.5</td>
<td>17.4</td>
</tr>
</tbody>
</table>

Decrease in size of target lesion from baseline
Increase in size of target lesion from baseline
Percentage change in size of target lesion contradicted by overall lesion response = progressive disease (denoted by *)

Fazio N et al., ENETS 2016
End points

- **Primary**: Proportion of patients with overall lesion assessment at month 9 being CR, PR, or SD according to RECIST v1.1
- **Key Secondary**: PFS, time to response, duration of response, objective response rate, best overall response, biochemical response rate, duration of biochemical response, biochemical PFS, safety, and tolerability

CR, complete response; CT, computed tomography; IM, intramuscular; MRI, magnetic resonance imaging; PFS, progression-free survival; PR, partial response; R, randomization; RECIST v1.1, Response Evaluation Criteria In Solid Tumors, version 1.1; SD, stable disease; WHO, World Health Organization.

Patients with advanced (unresectable or metastatic), typical and atypical carcinoid tumors of the lung/thymus

- Radiologic disease progression within 12 months
- All treatment lines, including treatment-naive
- WHO performance status ≤2

Randomized patients were locally assessed for efficacy by triphasic CT/MRI every 3 months for the duration of the core phase (12 months) and, if continued into the extension phase, every 3 months thereafter.
LUNA Trial: population

<table>
<thead>
<tr>
<th></th>
<th>All patients (N=124)</th>
<th>Pasireotide LAR (n=41)</th>
<th>Everolimus (n=42)</th>
<th>Pasireotide LAR + everolimus (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histologic grade</strong>a, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical carcinoid</td>
<td>39 (31.5)</td>
<td>14 (34.1)</td>
<td>12 (28.6)</td>
<td>13 (31.7)</td>
</tr>
<tr>
<td>Atypical carcinoid</td>
<td>85 (68.5)</td>
<td>27 (65.9)</td>
<td>30 (71.4)</td>
<td>28 (68.3)</td>
</tr>
<tr>
<td><strong>Primary tumor, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>116 (93.5)</td>
<td>38 (92.7)</td>
<td>39 (92.9)</td>
<td>39 (95.1)</td>
</tr>
<tr>
<td>Thymus</td>
<td>8 (6.5)</td>
<td>3 (7.3)</td>
<td>3 (7.1)</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td><strong>Functional status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functioning</td>
<td>28 (22.6)</td>
<td>12 (29.3)</td>
<td>7 (16.7)</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>Non-functioning</td>
<td>96 (77.4)</td>
<td>29 (70.7)</td>
<td>35 (83.3)</td>
<td>32 (78.0)</td>
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<tr>
<td><strong>Current metastatic extent</strong>b, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Liver</td>
<td>95 (76.6)</td>
<td>30 (73.2)</td>
<td>34 (81.0)</td>
<td>31 (75.6)</td>
</tr>
<tr>
<td>Bone</td>
<td>69 (55.6)</td>
<td>32 (78)</td>
<td>15 (35.7)</td>
<td>22 (53.7)</td>
</tr>
<tr>
<td>Lung</td>
<td>48 (38.7)</td>
<td>15 (36.6)</td>
<td>13 (31.1)</td>
<td>20 (48.8)</td>
</tr>
<tr>
<td>Cervical/thoracic lymph nodes</td>
<td>38 (30.6)</td>
<td>14 (34.1)</td>
<td>15 (35.7)</td>
<td>9 (22.0)</td>
</tr>
<tr>
<td>Pleura</td>
<td>10 (8.1)</td>
<td>2 (4.9)</td>
<td>2 (4.8)</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>Otherc</td>
<td>79 (63.7)</td>
<td>28 (68.3)</td>
<td>24 (57.1)</td>
<td>27 (65.8)</td>
</tr>
</tbody>
</table>

LAR, long-acting release.
aReconciled rates. During the randomization process, 7 patients were misstratified by the investigational sites with respect to histologic grade.
bIncluding individual sites with >10% involvement in at least 1 treatment group.
cIncluding skin, thyroid, kidney, adrenal, testis, ovary, breast, ascites (malignant), peritoneum, para-aortic abdominal lymph nodes, pancreas, spleen, brain, bone marrow, abdomen lymph node, paravertebral lymph node, subcutaneous lesions, supraclavicular lymph nodes, mediastinum, lung nodes, left supraclavicular adenopathy, right retrocrural lymph node, or soft tissue on anterior abdominal wall.
## LUNA: PROGRESSION FREE RATE AT 9 MONTHS

<table>
<thead>
<tr>
<th></th>
<th>Pasireotide LAR (n = 41)</th>
<th>Everolimus (n = 42)</th>
<th>Pasireotide LAR + everolimus (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>95% CI</td>
<td>n (%)</td>
</tr>
<tr>
<td>Proportion of patients</td>
<td>16 (39.0)</td>
<td>24.2-55.5</td>
<td>14 (33.3)</td>
</tr>
<tr>
<td>progression free at month 9(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum number of progression-</td>
<td>13</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>free patients to reject H(_0)(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Proportion of patients with overall lesion assessment at month 9 being CR, PR, or SD according to RECIST v1.1
- Conservative design of study may have resulted in underestimation of the response rates

CI, confidence interval.

\(^a\)Proportion of patients with overall lesion assessment at month 9 being CR, PR, or SD according to RECIST v1.1. Patients with missing or unknown month 9 assessment and with CR, PR, or SD at any of the following assessments at Week 48 or 52 are considered as progression free at month 9.

\(^b\)H\(_0\): Progression-free rate ≤20% is the null hypothesis on the proportion of patients progression free at month 9. The minimum number of progression-free patients to reject H\(_0\) is calculated according to the Fleming single-stage design.
TUMOR RESPONSE

Waterfall plot for best percentage change from baseline in sum of longest diameter (FAS)

Pasireotide LAR (N = 41, n = 36)\textsuperscript{a}

- Decrease 30.6% (11)
- Zero change 11.1% (4)
- Increase 38.9% (14)
- *Contradiction 19.4% (7)

Everolimus (N = 42, n = 33)\textsuperscript{a}

- Decrease 48.5% (16)
- Zero change 12.1% (4)
- Increase 30.3% (10)
- *Contradiction 9.1% (3)

Pasireotide LAR and Everolimus (N = 41, n = 33)\textsuperscript{a}

- Decrease 72.7% (24)
- Zero change 12.1% (4)
- Increase 12.1% (4)
- *Contradiction 3.0% (1)
LUNA : progression free survival per investigator review

Kaplan-Meier median progression-free survival
P arm: 8.51 months (95% CI: 5.68-NE)
E arm: 12.48 months (95% CI: 5.55-NE)
EP arm: 11.79 months (95% CI: 11.10-NE)
Conclusions

- Treatment of advanced pulmonary carcinoid is based on expert multidisciplinary staff decision and guidelines: it includes watch-and-see strategy, surgery/locoeregional options, systemic options.
- Time has come for pulmonary carcinoid dedicated trials: SPINET ongoing.
- Everolimus is the first approved agent for the treatment of advanced, progressive, well-differentiated, non-functional NET of lung and gastrointestinal origin (FDA, EMA) based on the results of Radiant 4.
- Options remains palliative; no recommendation for adjuvant therapy.
- Active translational research expected.
- Similar strategy are used for advanced thymic carcinoids.