Thoracic neuroendocrine tumors: update

Eric Baudin

Gustave Roussy, Villejuif, France
DISCLOSURE INFORMATION – ERIC BAUDIN

- Personal financial interests
  Expert board: Ipsen, Novartis, AAA, Pfizer - Drug supply: Pfizer, AAA

- Institutional financial interests
  Research grant: Novatis, HRA - Principal investigator: Ipsen

- Non-financial interests, Leadership role:
  President of the french group of endocrine tumors (GTE)
  Coordinator of the french neuroendocrine and adrenal cancer networks
  Advisory board of ENSAT and ENETS Networks
NET diagnosis
endocrine morphology and postitive Chromogranine A /synaptophysine staining
Epidemiology of NENs: Pulmonary Is the Most Frequent Primary (25%)
What the clinician should know:

- A rare entity
- Specific multifaceted characteristics
- Long-term survival
- A few trials and different targets
Thoracic Medical Oncologist’s View on the Overall Proportion of Lung Malignancies

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>75%</td>
</tr>
<tr>
<td>SCLC</td>
<td>20%</td>
</tr>
<tr>
<td>TC</td>
<td>2%</td>
</tr>
<tr>
<td>LCNEC</td>
<td>3%</td>
</tr>
<tr>
<td>AC</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Incidence: 0.2 to 2/100,000 persons per year in both the United States and Europe.

AC, atypical carcinoid; LCNEC, large-cell neuroendocrine carcinoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; TC, typical carcinoid.

Pulmonary carcinoids:
specific multifaceted characteristics

- WHO Classification 2015
- pTNM UICC 8th edition, 2017
- Preinvasive/neoplastic conditions: DIPNECH, multiple endocrine neoplasia type 1
- Functioning syndrome (echocardiography)
- Chromogranin A levels (5HIAA, ACTH/Cortisol, GhRh/Gh)
- Somatostatin receptor imaging/PET (PET FDG if SRI negative or ,AC)

DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; ENETS, European Neuroendocrine Tumor Society; ESMO, European Society for Medical Oncology; FDG, fluorodeoxyglucose; NANETS, North American Neuroendocrine Tumor Society; PET, positron emission tomography; PTH, parathyroid hormone; UICC, International Union Against Cancer.
### WHO Classification 2015: Two Entities Within One Category

<table>
<thead>
<tr>
<th>WHO</th>
<th>Typical carcinoid ≥5 mm</th>
<th>Atypical carcinoid</th>
<th>Large-cell neuroendocrine carcinoma</th>
<th>Small-cell neuroendocrine carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td>Carcinoid</td>
<td>Carcinoid</td>
<td>NE morphology CGA/SYN+</td>
<td>NE morphology</td>
</tr>
<tr>
<td><strong>Cytological features cell size</strong></td>
<td>–</td>
<td>–</td>
<td>Non-small cell &gt;20 µm (3L)</td>
<td>Small cell &lt;20 µm (3L)</td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td>No</td>
<td>No, focal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Mitoses / 2 mm²</strong></td>
<td>&lt;2</td>
<td>2–10</td>
<td>&gt;10 Median, 70</td>
<td>&gt;10 Median, 80</td>
</tr>
<tr>
<td><em><em>Differential diag.</em> Ki67</em>*</td>
<td>Up to 5%</td>
<td>Up to 20%</td>
<td>40–80%</td>
<td>50–100%</td>
</tr>
</tbody>
</table>

CGA, chromogranin A; NE, neuroendocrine; SYN, synaptophysin.

*Among other criteria.

High grade AC (Lung NET G3): new entity: 5%, treat like AC
Prognosis of metastatic pulmonary carcinoids

Overall survival

- The median OS 6.7 yrs (CI 95%: 62-99)
- OS at 5 and 10 years: 60.2% and 24.5%

<table>
<thead>
<tr>
<th>Number of prognostic factors</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ou 1 factor</td>
<td>8.7 yrs *</td>
</tr>
<tr>
<td>2 factors</td>
<td>4.5 yrs</td>
</tr>
<tr>
<td>3 ou 4 factors</td>
<td>2.7 yrs</td>
</tr>
</tbody>
</table>

*Typical carcinoid: Median OS 104.6 mois – 8.7 year
Atypical carcinoid Median OS 65.1 months – 5.4 years

Robelin P et al JTO 2019: survival of 162 metastatic lung carcinoids, 76% are SRS positive
Lung carcinoids: targets
72% mutations affect a small set of pathways

Gene copy number (54 pts), genome/exome (44 pts) and transcriptome (69 pts) sequencing
No clinical characterization

Low mutation frequency: 0.4 mutations/Mb
Candidate drivers genes
- 40% Histone Covalent Modifiers (MEN1..)
- 20% ATP-dep.SWI/SNF chromatin remodeling (ARID1A...)
- 17% E3 ubiquitin ligases (EIF1AX...)
- 2 cases with Rb or p53 mutation
No genetic segregation between typical and atypical carcinoids

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Lung carcinoid targets are different from SCLC and NSCLC!

**SCLC-like?**

- No p53/Rb concurrent alterations in carcinoids
- Common alterations Atypical Ca.-Large Cell (epigenetic/mTOR) reported: clinical relevance?
  - Vollbrecht C et al. BJC 2015
  - Fernandez-Cuesta L et al Nat Com 2017
  - Simbolo M et al J Pathol 2017, JTO 2019
  - Pelosi G Virch Arch 2018

**NSCLC-like?**

- Very rare alterations: EGFR, ErbB2, ALK, c-MET, RET, KRAS, BRAF
  - Mengoli MC et al. AJSP 2018
  - Rickman O et al. CCR 2009
  - Nakamura JCP et al JCP 2013
  - Vootmal J et al NET
  - Komminothh et al JCEM 1996
  - Armengol G et al Lung 2015
  - Najakima M 2017, Wang V 2017
  - Fukuizumi A 2015, Zheng Q 2018
  - Liu N 2019: 4/5 objective response in AC with ALK reaaffangement
Surgery is the only curative modality

**TYPICAL CARCINOID**
- Conservative anatomical resection
- Segmentectomy, Lobectomy
- Bronchoplastic/sleeve resection
- Lymph node dissection
- R0 resection > 95%

**ATYPICAL CARCINOID**
- Lobectomy (no wedge)
- Lymph node dissection
- R0 resection > 90%

**R status, number of N, stations sampled**

Raz D et al Lung Cancer 2015: 4111 pts with TC N0, SEER
Huang Y et al 2018 Cancer Medicine: 7057 pts including 503 AC, SEER,
Lung carcinoids: no indication for routine adjuvant therapy

Nussbaum DP et al 2015: 4612 CT including 629 N positives (13%) including 35 adjuvant treatments (6%)
Analysis adjusted to comorbidity, age, T and nN ...

Anderson KL 2017: 581 AC including 38% N1 including 41% of adjuvant treatments;
Adjusted analysis: age, morbidity, T, surgery
Lung carcinoids: adjuvant therapy in guidelines

**ENETS 2015**
- In case of N2-AC
- MDT case by case discussion
- No selected option

**NCCCN 2019**
- In stage IIIA - AC
- Platinum-based + EBRT
- Temozolomide
ENETS guidelines 2015: palliative setting
decision is driven by the presence of functioning syndrome and prognosis

No dedicated phase III trial, No predictor of response, Very good prognosis in subgroups
Everolimus: the only EMA / FDA approved agent
NCCN guidelines 2019
Same options but platin-based chemo. proposed as first line option
Principles of therapeutic management: palliative setting

Hormone
- Symptomatic
- Tumour debulking

Tumour
- Watch and see/Locoregional
- Systemic

Medical management of lung carcinoids is extrapolated from digestive NET
Pulmonary Carcinoids Secrete Hormones: Specific Characterization and Treatment

Chromogranin A + glucose/K + additional tests (5-HIAA, ACTH, GHRH...) + calcium (MEN1 screening), echocardiography...

ACTH, adrenocorticotropic hormone; GHRH, growth hormone-releasing hormone; 5-HIAA, 5-hydroxyindoleacetic acid; MEN1, menin/multiple endocrine neoplasia 1.
Lung carcinoid syndrome: treatments up to 40% of advanced lung carcinoid patients

- **First line**
  - Long acting somatostatin analogues: Octreotide LAR 30 mg or Lanreotide 120 mg / 4 weeks
  - Short acting octreotide as rescue or in perioperative conditions

- **Second line: refractory carcinoid syndrome (RCS)**
  - Slowly progressive and small tumor burden
    - Increase of somatostatin analogue dosage
    - Interferon
    - Serotonin synthesis inhibitor, telostristat ethyl: only drug approved for the treatment of diarrhea of RCS (FDA)
  - Slowly progressive and high tumor burden
    - Tumor debulking: surgery and/or locoregional therapies
    - PRRT
  - Rapidly progressive
    - Everolimus
    - Chemotherapy
Principles of therapeutic management: palliative setting

Hormone
- Symptomatic
- Tumour debulking

Tumour
- Watch and see/Locoregional
- Systemic
High expression of sstr 2 in typical carcinoid

an historical target of well differentiated low grade NET

Somatostatin analogues in lung carcinoids: only retrospective studies and ...LUNA trial

- Sullivan I et al. EJC 2017: OCTREOTIDE LAR or LANREOTIDE (67pts)

  Median PFS = 17.4 months [95% CI = 8.7–26.0]

- Ferrola P et al ESMO 2016: LUNA trial, PASIREOTIDE (41 pts)

  9 months - PFR = 39%
Somatostatin analogues are recommended in slowly progressive somatostatin receptor positive pulmonary carcinoids.
SPINET: failure (insufficient enrolment) means feasibility of phase III questioned in lung carcinoids, still!

- 216 PATIENTS

- Screening/Baseline
- Randomize
- Lanreotide Autogel/Depot
  - 120 mg deep SC inj every 4 weeks + BSC
- 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

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 open-label treatment
- Does not request to enter or meet criteria for open-label treatment

NCT02683941

When recommendations hamper active enrollment ….
Somatostatine receptor imaging prior to SSA and PRRT sequence
Peptide Receptor Radionuclide Therapy

Vectorized internal radiotherapy

Surexpression SSTR2 sur les TNE
Internalisation du SSTR2 suite au traitement par octreotide radiomarqué
Pas d’internalisation avec antagoniste

Oberg et al, GASTROENTEROLOGY 2010
**PRRT-Lu in advanced bronchial NETS**

*selected patients with positive SRI, evaluation every 2-12 months*

<table>
<thead>
<tr>
<th>Studies/design</th>
<th>n</th>
<th>Population</th>
<th>PR-RECIST/SWOG</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imhof A 2011 Retrospective / DOTATOC</td>
<td>84</td>
<td>Progressive -12 mo.</td>
<td>45%*</td>
<td>NA**</td>
</tr>
<tr>
<td>Ianniello A 2015 Phase II / DOTATATE</td>
<td>34</td>
<td>Progressive -12 mo</td>
<td>29%***</td>
<td>18.5 mo. median</td>
</tr>
<tr>
<td>Mariniello A 2016 Retrospective/Mixed</td>
<td>114</td>
<td>78% progressive</td>
<td>13%</td>
<td>31-46% at 3 yrs</td>
</tr>
<tr>
<td>Brabander 2017 Retrospective****/DOTATAT</td>
<td>23</td>
<td>16-54% progressive</td>
<td>30%</td>
<td>20 mo. median</td>
</tr>
</tbody>
</table>

*42% of RECIST evaluation, **TTP in the all 1109 pts, no available per primary, *** SWOG criteria, **** Not ITT*
PRRT-Lu in advanced bronchial NETS

*Higher response rate in Typical Carcinoids*

<table>
<thead>
<tr>
<th></th>
<th>Lung</th>
<th>n</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>mPFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>34</td>
<td>3%</td>
<td>12%</td>
<td></td>
<td>47%</td>
<td>38%</td>
<td>18.5</td>
</tr>
<tr>
<td>TC</td>
<td>15</td>
<td>6%</td>
<td>27%</td>
<td></td>
<td>47%</td>
<td>20%</td>
<td>20.1</td>
</tr>
<tr>
<td>AC</td>
<td>19</td>
<td>0%</td>
<td>0%</td>
<td></td>
<td>47%</td>
<td>53%</td>
<td>15.7</td>
</tr>
</tbody>
</table>

Ianniello A et al. EJNM 2015: TC, PET FDG and TTF1 negative results are prognostic

Netter-01 trial in midgut target patients with good prognosis: 73% G1, RECIST progressive over 1-3 yrs (3.8-4.8 yrs after diagnosis, 62% <25% liver-11% bone-15% mesenteric involvement, 5-HIAA X 2-3 UNR (no predictor)

Ezzidin S et al. EJNMI 2011: 81 pts, mSWOG at 3 months is higher in G1
Lung carcinoids: chemotherapy (Temozolomide for ENETS/ESMO) is recommended in aggressive tumors

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Non-responder</th>
<th>Responder</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-pancreatic</td>
<td>73 (77.7)</td>
<td>21 (22.3)</td>
<td>0.016</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>48 (60.8)</td>
<td>31 (39.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Ki-67</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENETS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki-67 \leq 2%</td>
<td>17 (94.4)</td>
<td>1 (5.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ki-67 3–\leq 20%</td>
<td>61 (73.3)</td>
<td>19 (23.8)</td>
<td></td>
</tr>
<tr>
<td>Ki-67 &gt;20%</td>
<td>43 (57.3)</td>
<td>32 (42.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;58</td>
<td>58 (68.6)</td>
<td>27 (31.4)</td>
<td>0.703</td>
</tr>
<tr>
<td>\geq 58</td>
<td>62 (71.3)</td>
<td>25 (28.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Performance status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30 (66.7)</td>
<td>15 (33.3)</td>
<td>0.712</td>
</tr>
<tr>
<td>1</td>
<td>74 (72.5)</td>
<td>28 (27.5)</td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>16 (66.7)</td>
<td>8 (33.3)</td>
<td></td>
</tr>
</tbody>
</table>

AUC is 0.66
Chemotherapy in carcinoids: phase III

Sun W et al. JCO 2005;23:4897-4904: 166 randomized carcinoids (22 bronchial)

Granberg 2001, Bajetta 2002: Fu-STZ in bronchial Carcinoids, ORR between 0-28%

Study | N (Lung Ca.) | Regimen | RR  
--- | --- | --- | ---
Moertel, 1979 | 118 (17) | STZ-Fu | 33%
 |  | STZ-CTX | 26%
Engstrom, 1984 | 172 (18) | STZ- FU | 22%

Moertel, 1979  
118 (17)  
STZ-Fu  
33%  
STZ-CTX  
26%

Engstrom, 1984  
172 (18)  
STZ- FU  
22%
Lung carcinoid: Objective response rate to chemotherapy and other options (number of patients, mPFS)

Robelin P et al JTO 2019: results of chemotherapy in 162 metastatic lung carcinoids, median follow-up 56 months
mTOR pathway alterations in pulmonary carcinoids: DNA mutations and CNA alterations

PI3K/AKT/mTOR mutations: 11.7% of carcinoids

RICTOR/PIK3 CNA-Gain: 48% of carcinoids

Simbolo M et al J Pathol 2017
## Everolimus: the most studied, the only approved

<table>
<thead>
<tr>
<th>Study (number of pts)</th>
<th>Trial</th>
<th>Decrease/Sd functioning</th>
<th>Number (%) of lung carcinoid</th>
<th>RP</th>
<th>SSP (mo)</th>
</tr>
</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>
</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>
</tr>
<tr>
<td>Yao J, 2016 (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>
</tr>
<tr>
<td>Ferrola P, 2017</td>
<td>LUNA Phase II - RM</td>
<td>Progressive-12 Functioning</td>
<td>116 (93%)</td>
<td>2%</td>
<td>TCR-9 mo 33-58%</td>
</tr>
</tbody>
</table>

* FDA and EMA approval in advanced progressive non-functional pulmonary and digestive NETS in 2016

RADIANT 4 validates everolimus in NET an aggressive population of NETs

- 30% lung
- 64% G1 or well differentiated (IP UK)
- Prior PD
- 76% liver <10% (bone, 19%)

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

No predictor emerged
## RADIANT 2-4: lung carcinoid subgroup analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LUNG NET RADIANT 4</strong></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>9.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>LUNG NET RADIANT 2</strong></td>
<td></td>
</tr>
<tr>
<td>Everolimus + Oc</td>
<td>13.6</td>
</tr>
<tr>
<td>Placebo + Oc</td>
<td>5.6</td>
</tr>
</tbody>
</table>

LUNA TRIAL: RANOMIZED PHASE II
FIRST PULMONARY/THYMIC CARCINOID DEDICATED TRIAL

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

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.

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: 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 progression free at month 9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16 (39.0)</td>
<td>24.2-55.5</td>
<td>14 (33.3)</td>
</tr>
<tr>
<td>Minimum number of progression-free patients to reject H&lt;sub&gt;0&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13</td>
<td></td>
<td>14</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.

<sup>a</sup>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.

<sup>b</sup>H<sub>0</sub>: 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<sub>0</sub> is calculated according to the Fleming single-stage design.
Metastatic lung carcinoids in 2019: hypothesis for stratifying?

- **Sstr positive**
  - homogenous/good prognosis
  - SSA
  - Protocols (safety) / PRRT (protocols)
  - Protocols (safety)

- **Sstr negative**
  - heterogenous/poor prognosis
  - Everolimus / protocols (efficacy)
  - Protocols (efficacy)
  - Chemotherapy

Good prognosis means PS0, low CGA<3.5, Typical carcinoid (proliferative index), positive SRS
What is ongoing?

**TKI**

Phase III ongoing (SANET-ep, CABINET, AXINET)
- Lung carcinoids as a subgroup of NET patients
- Xu JM et al ESMO 2019

**Immunotherapy**

PD1 inhibitor: Spartalizumab (PDR 001)
- Yao J et al ESMO 2018: 20% ORR (6/30 lung carcinoids)
- Median fup: 6 months
- Other trials: DUNE, Nivolumab + PRRT...

**Epigenetic**

Lysine Specific Demethylase 1 inhibitor CC 90011
- Hollebecque A et al ESMO 2019
SURUFATINIB (SULFATINIB)
Phase 1-2 multicentric suggested efficacy and tolerability in progressive extrapancreatic NET

Table 1: Sulfatinib kinase selectivity profile

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR 1</td>
<td>0.002</td>
</tr>
<tr>
<td>VEGFR 2</td>
<td>0.024</td>
</tr>
<tr>
<td>VEGFR 3</td>
<td>0.001</td>
</tr>
<tr>
<td>FGFR1</td>
<td>0.015</td>
</tr>
<tr>
<td>CSF1R</td>
<td>0.004</td>
</tr>
<tr>
<td>TrkB</td>
<td>0.041</td>
</tr>
<tr>
<td>FLT3</td>
<td>0.067</td>
</tr>
<tr>
<td>278 other kinases</td>
<td>&gt;0.150</td>
</tr>
</tbody>
</table>

FLT3: fins-related tyrosine kinase 3; IC$_{50}$: half maximal inhibitory concentration; TrkB: tropomyosin receptor kinase B.
SANET-ep: PHASE III STUDY DESIGN

Study population
Progressive, advanced extrapancreatic NET

Randomization: 2:1
Stratification factors
- Treated or naïve
- Pathological grade 1 or 2
- Tumor origins A, B or C

Surufatinib
300mg QD

Placebo

Survival follow up

Primary Endpoint:
- Investigator-assessed PFS

Secondary Endpoints:
- ORR, DCR, DoR, TTR, OS
- Safety and tolerability

Open-label surufatinib

PD

PD

- Statistical assumption: 273 patients planned based on the assumption of the median PFS of 8 months in placebo arm, HR of surufatinib treatment is 0.6 with a two sided alpha 0.05.
- Interim analysis was planned when 127 PFS events (i.e. 70% of the planned PFS events for final analysis) were observed; study early termination for superiority ($p < 0.015$) was allowed.
- Tumor evaluation was conducted by investigators; a blinded independent image review committee (BIIRC) performed tumor assessment retrospectively in parallel, which was used for sensitivity analysis of PFS.

Tumor origin: A: jejunum, ileum, duodenum, thymus, cecum; B: lung, stomach, liver, appendix, colon, rectum; C: others or unknown origin.
INVESTIGATOR-ASSESSED PFS (PRIMARY)

SANET-ep clearly succeeded in meeting the superiority criteria of PFS

BIRC-assessed PFS:
HR: 0.657 (p=0.037)

BIRC-adjudicated PFS, post-hoc:
HR: 0.570 (p=0.0065)
ORR: 10% (p=0.0051)
DCR: 86.5% (p=0.0022)

Primaries:
- GI 47%
- Lung 9%
- UK 14%
- Others 29%
PDR001 Study Design

**Patients Key Eligibility Criteria:**

- Advanced or metastatic well-diff (grade 1 or 2), nonfunctional thoracic, GI or panNET and poorly-diff GEP NEC
- ECOG Performance Status 0-2
- Any PD-L1 expression in tumor or immune cells
- Measurable disease (RECIST 1.1)
- Prior treatment with everolimus required for lung and GI NET. Everolimus not mandatory for thymic NET. Sunitinib and/or everolimus required in panNET
- At least 1 prior chemotherapy regimen per investigator’s choice in GEP NEC patients

**N=110 (Planned)**

- Well-diff GI Cohort (n=30)
- Well-diff Pancreatic Cohort (n=30)
- Well-diff Thoracic (lung + thymic) Cohort (n=30)
- Poorly-diff CEP NEC Cohort (n=20)

**Primary endpoint:**
- Confirmed ORR (per BICR)

**Secondary endpoints (main):**
- DoR (per BICR; key secondary)
- PFS
- Overall survival
- Efficacy by irRECIST
- Safety
- Quality of life
- Change in CgA and NSE
- Pharmacokinetics

**Treatment:**
Spartalizumab 400 mg IV q4w until confirmed PD, intolerable toxicity, or patient withdrawal

Primary efficacy analysis is planned 12 months after the first treatment of last patient in the well diff NET cohort

Abbreviations: BICR, blinded-independent central review; CgA, chromogranin A; diff, differentiated; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; GEP NEC, gastrointestinal; ir, immune-related; IV, intravenous; NET, neuroendocrine tumors; NSE, neuron specific enolase; ORR, overall response rate; panNET, pancreatic NET; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; pts, patients; q4W, every 4 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.
**PD1 INHIBITOR : SPARTALIZUMAB (PDR 001) PHASE II TRIAL**  
Yao J et al ESMO 2018

<table>
<thead>
<tr>
<th>Variable</th>
<th>Well-diff NET</th>
<th>Poorly-diff GEP NEC N=21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thoracic cohort N=30</td>
<td>Pancreatic cohort N=33</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>6 (20)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>16 (53)</td>
<td>17 (52)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>5 (17)</td>
<td>13 (39)</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>3 (10)</td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>Confirmed ORR, n (%)</strong></td>
<td><strong>6 (20)</strong>*</td>
<td><strong>1 (3)</strong>***</td>
</tr>
<tr>
<td>DCR, n (%)</td>
<td>22 (73)</td>
<td>19 (58)</td>
</tr>
</tbody>
</table>

*Among 6 responders in thoracic cohort, all were in patients with atypical carcinoids, 4 responses were ongoing with duration of response of 2-6 months. 2 other patients died after confirmation of response due to respiratory failure (not treatment-related) and myasthenia gravis (treatment-related). 11 PR in the GI cohort with time to response of approx. 7 months was unconfirmed at the time of the cut-off date.

Abbreviations: BICR, blinded-independent central review; DCR, disease control rate; diff, differentiated; GEP NEC, gastroenteropancreatic neuroendocrine carcinoma; NET, neuroendocrine tumors; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Median follow-up, months (range): 8 (6.0-10.9) for NET and 6 (4.7-6.9) for NEC
PHASE 1 CC 90011 LYSINE DEMETHYLASE 1 INHIBITOR

Hollebecque A et al

Maximum tolerated dose: 80 mg QW
DLT: Grade 3-4 thrombocytopenia
RP2D: 60 mg QW
Expansion cohort: reversible side effects (thrombocytopenia, neutropenia, asthenia)
Phase 1 CC 90011 Lysine Demethylase 1 inhibitor
11/23 bronchial NEN with SD > 6 months (CGA decrease >30% 11/20pts)

Table 1. CC-90011-ST-001: Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Enrolled Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Part A (n = 200)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>61 (22-75)</td>
</tr>
<tr>
<td>&gt; 65 y, n (%)</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>26 (52)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19 (38)</td>
</tr>
<tr>
<td>1</td>
<td>31 (62)</td>
</tr>
<tr>
<td>Tumor stage IV at enrollment (solid tumors), n/N (%)</td>
<td>43/40 (88)</td>
</tr>
<tr>
<td>No. of prior systemic cancer therapies, median (range)</td>
<td>3 (1-9)</td>
</tr>
<tr>
<td>Tumor type, n (%)</td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td>49 (98)</td>
</tr>
<tr>
<td>NEN/NEC</td>
<td>27 (54)</td>
</tr>
<tr>
<td>Bronchial</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Prostate</td>
<td>5 (10)</td>
</tr>
<tr>
<td>SCLC</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (22)</td>
</tr>
<tr>
<td>NHL</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Figure 3. CC-90011-ST-001: Duration of Treatment in Patients With NENs and NECs

Hollebecque A et al ESMO 2019

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Thymic carcinoid

- <0.5% of NET
- Predominance in male patients
- Same characterisation than lung carcinoid but
  - Higher frequency of atypical carcinoid, Cushing syndrome, MEN1 (98% men, up to 25% in retrospective studies)
  - Most advanced stage analyzed by TNM or Masaoka-Koga used for staging
- Prognosis is 28-72% at 5-years mainly influenced by stage and R status
- Only, 50% of R0 resection (guidelines for thymic surgery, lymph node resection recommended)
- Same therapeutic management than lung carcinoids
Lung carcinoid management: conclusions

- Dedicated management and networks: French GTE-ENDOCAN, ENETS, ENDOCAN

- 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 which remains palliative

- Time has come for pulmonary carcinoid dedicated trials: randomized phase II, feasibility of phase III? Feasibility of adjuvant trial?

- 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

- New options: TKI, immunotherapy/epigenetic? active translational research expected

- Similar strategy are used for advanced thymic carcinoids