CLINICAL MANAGEMENT OF HIGH-GRADE GEP NENS

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The Christie ENETS Centre of Excellence
Manchester, UK

ESMO Advanced Course | 14-15 June 2019
DISCLOSURES

Travel Grant
Celgene, Ipsen, Novartis, NuCana

Speakers’ Bureau
Abbott, Celgene, Ipsen, Novartis, Pfizer, Sirtex

Consulting or Advisory Role
Abbott, Agios, AstraZeneca, Baxalta, Bioven, Celgene, Delcath, Genoscience Pharma, Incyte, Ipsen, Keocyt, Lilly, Merck, MidaTech, Mundipharma, Novartis, NuCana, PCI Biotech, Pfizer, Pieris Pharmaceuticals, QED Pharmaceuticals
LEARNING OBJECTIVES

By the end of this presentation, attendees should:

1. Understand the requirements for diagnosis of HG-NEC
2. Be able to adequately stage patients
3. Be conversant with first-line chemotherapy
4. Understand limitations of second-line chemotherapy
5. Be introduced to the emerging role of immunotherapy
6. Understand issues around heterogeneity
NECs have an aggressive natural history that is characterized by early, widespread metastases

From the Netherlands Cancer Registry

- Annual incidence of GEP NEC is approx. **0.54 per 100,000 population**
- **Large cell** GEP NEC is twice as common as **small cell** GEP NEC (incidence of 0.36 versus 0.18 per 100,000 population)
- There was an **increase in incidence** of GEP NECs over the last two decades from 0.3 to 0.54 per 100,000

BUT PATIENTS PRESENT LIKE THIS....

64-year old male

April 2018 - Presented with symptoms of bowel obstruction

Underwent emergency right hemicolectomy

**Histology** pT3 pN1 pMX poorly differentiated neuroendocrine carcinoma of the caecum; Ki67 60%

CT scan demonstrated liver metastases

➢ Referred to Medical Oncology
BIOPSY IS TAKEN
Which classification?

2017 - WHO Classification of Endocrine Tumors introduced the PanNET G3 category
2010 - WHO Classification of Digestive Tumors included the ENETS Ki67-based proliferation grading system
2007 - ENETS proposed a Ki67-based proliferation grading system for midgut and hindgut NENs (Rindi et al., 2007 [44])
2006 - ENETS proposed a Ki67-based proliferation grading system for foregut NENs (Rindi et al., 2006 [43])
2004 - WHO Classification of Endocrine Tumors included Ki67 as a prognostic marker into the PanNETs classification
2000 - WHO Classification of Tumors of the Digestive System included Ki67 as a prognostic marker
2000 - WHO Classification of Endocrine Tumors introduced Ki67 in the classification of PanNETs
1996 - First reports on the prognostic role of Ki67 index in PanNENs using the MIB1 antibody (La Rosa et al., 1996 [22] and Pelosi et al., 1996 [37])
1983 - Generation of the monoclonal antibody Ki67
1980 - WHO Classification of Endocrine Tumors was not correlated with clinical behavior
HIGH Ki67 IS NOT THE SAME AS HIGH-GRADE

<table>
<thead>
<tr>
<th>2010 WHO GEP NEN</th>
<th>Ki67 index</th>
<th>Mitotic index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Well differentiated NENS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NET G1</td>
<td>≤ 2%</td>
<td>&lt; 2/20 HPF</td>
</tr>
<tr>
<td>NET G2</td>
<td>3–20 %</td>
<td>2–20/10 HPF</td>
</tr>
<tr>
<td><strong>Poorly differentiated NENs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC G3</td>
<td>&gt; 20%</td>
<td>&gt; 20/10 HPF</td>
</tr>
</tbody>
</table>

Mixed adenoneuroendocrine carcinoma (MANEC)

My patient has a Ki67% of 30% but it looks well differentiated

2010 classification: NEC G3

NET, neuroendocrine tumour; NEC, neuroendocrine carcinoma; HPF, high power fields
HIGH Ki67 IS NOT THE SAME AS HIGH-GRADE

<table>
<thead>
<tr>
<th>2010 WHO GEP NEN</th>
<th>Ki67 index</th>
<th>Mitotic index</th>
<th>2017 WHO pancreas NEN</th>
<th>Ki67 index (% of &gt;500 cells)</th>
<th>Mitotic index (2 mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Well differentiated NENS</strong></td>
<td></td>
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</tr>
<tr>
<td>NET G1</td>
<td>≤ 2%</td>
<td>&lt; 2/20 HPF</td>
<td>NET G1</td>
<td>&lt; 3%</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>NET G2</td>
<td>3–20%</td>
<td>2–20/10 HPF</td>
<td>NET G2</td>
<td>3–20%</td>
<td>2–20</td>
</tr>
<tr>
<td><strong>Poorly differentiated NENs</strong></td>
<td></td>
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</tr>
<tr>
<td>NEC G3</td>
<td>&gt; 20%</td>
<td>&gt; 20/10 HPF</td>
<td>NEC G3</td>
<td>&gt;20%</td>
<td>&gt; 20</td>
</tr>
<tr>
<td><strong>Mixed adenoneuroendocrine carcinoma (MANEC)</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Mixed NE non-NE neoplasm (MiNEN)</td>
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</tbody>
</table>

NET, neuroendocrine tumour; NEC, neuroendocrine carcinoma; HPF, high power fields.
HIGH Ki67 IS NOT THE SAME AS HIGH-GRADE

“A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal

“NET G3” only applies to pancreatic NENs
Likely to extend to other NENs – not yet implemented
Morphology first

Well-differentiated
Poorly-differentiated

Ki67 second

Grade 1
Grade 2
Grade 3
IMPORTANCE OF GRADE

**ENETS | 1072 patients with pancreatic NETs¹**

**USA | 425 patients with pancreatic NETs²**

**STAGING**

**Morphology first**
- Well-differentiated
- Poorly-differentiated

**Ki67 second**
- Grade 1
- Grade 2
- Grade 3

**Staging**
- CT scan
- MR scan
- FDG-PET
SYSTEMIC CHEMOTHERAPY IN HG-NECs
ROLE OF CHEMOTHERAPY IN **INTESTINAL** NENS

- **CS**
  - Refractory CS and SD
    - Octreotide or Lanreotide
    - Consider debulking surgery of LM (see fig. 1)
  - Refractory CS and/or PD
    - Consider locoregional/ablative therapy (see fig. 1)
      - or SSA dose increase
      - or add-on IFN-alpha 2b
      - or pasireotide or a clinical trial
      - or PRRT

- **Advanced loco-regional disease or distant metastases**
  - Complete resection if feasible (G1/G2)
    - Resect primary and metastases (see fig. 1)
  - **Non-functional (G1, low tumor burden, no symptoms, SD)**
    - Watch and wait or Octreotide or lanreotide
      - → PD →
      - or locoregional therapy
      - or PRRT (if SSTR positive)
      - or everolimus
      - or IFN-alpha 2b
  - **Non-functional (G2 and/or high tumor burden, or PD or symptoms)**
    - Octreotide or lanreotide
    - SSTR negative
      - Everolimus or IFN-alpha or Locoregional therapy
  - **NEC, G3**
    - Cisplatin and Etoposide
      - → PD →
      - FOLFOX or FOLFIRI or TEM/CAP or Clinical trial

Pavel et al Neuroendocrinology 2016;103:172–185
ROLE OF CHEMOTHERAPY IN PANCREATIC NENs

- **Advanced loco-regional disease or distant metastases**
  - **Functional activity**
    - Consider debulking surgery of LM (see fig. 1)
  - **Complete resection if feasible (G1/G2)**
    - Resect primary and metastases (see fig. 1)
  - **Non-functional (G1, low G2, low tumor burden, SD or initial diagnosis, no symptoms)**
    - Lanreotide (octreotide) or Watch and wait
      - Lanreotide (octreotide)
        - Everolimus or sunitinib or cytotoxic chemotherapy#
          - PRRT or 2nd-line CTX or Clinical trial
      - Everolimus or Sunitinib
  - **Non-functional (G2, high tumor burden, and/or PD or symptoms)**
    - Cytotoxic chemotherapy#
      - PD
  - **G3 NEN**
    - Cisplatin† + Etoposide or STZ/5-FU or TEM/CAP
      - PD
  - **G3 NEC or G3 NET**
    - FOLFOX or FOLFIRI or Clinical trial

Pavel et al. Neuroendocrinology 2016;103:172-185
Systemic chemotherapy with a **platinum-based combination regimen** is recommended in the first-line advanced setting, analogous to that used for small cell lung cancer\(^1\).

**IHC:**
- CD56 +
- Synaptophysin +
- High Ki-67

**Key molecular/genomic aberrations:**
- p53 over expression
- Rb loss

Systemic chemotherapy with a platinum-based combination regimen is recommended in the first-line advanced setting, analogous to that used for small cell lung cancer. 


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**...BUT WHICH “PLATINUM ETOPOSIDE”?**

Survey of practice

UK
Spain
Italy
France
Sweden
Netherlands
Greece
Germany
Denmark
Belgium
USA

---

1. Cisplatin (75 mg/m² on day 1) with **IV etoposide** (120 mg/m² IV for 3 days) 3-weekly
   - Responses: 2.7%
   - n: 2

2. Cisplatin (100 mg/m² on day 1) with **IV etoposide** (120 mg/m² IV for 3 days) 3-weekly
   - Responses: 6.9%
   - n: 5

3. Cisplatin (75 mg/m² on day 1) with **IV etoposide** (100 mg/m² IV for 3 days) 3-weekly
   - Responses: 23.3%
   - n: 17

4. Cisplatin (100 mg/m² on day 1) with **IV etoposide** (100 mg/m² IV for 3 days) 3-weekly
   - Responses: 5.5%
   - n: 4

5. Cisplatin (25 mg/m² on day 1, 2 and 3) with **IV etoposide** (100 mg/m² IV for 3 days) 3-weekly
   - Responses: 1.4%
   - n: 1

6. Cisplatin (25 mg/m² on day 1, 2 and 3) with **IV etoposide** (120 mg/m² IV for 3 days) 3-weekly
   - Responses: 2.7%
   - n: 2

7. Cisplatin (100 mg/m² on day 1) with **IV etoposide** (100 mg/m² IV on day 1) followed by **oral etoposide** (200 mg/m² on days 2 and 3) 3-weekly
   - Responses: 2.7%
   - n: 2

8. Cisplatin (100 mg/m² on day 1) with **IV etoposide** (100 mg/m² IV on day 1) followed by **oral etoposide** (200 mg/m² on days 2 and 3) ever3-weekly
   - Responses: 0.0%
   - n: 0

9. Cisplatin (100 mg/m² on day 1) with **oral etoposide** (200 mg/m² on days 1, 2 and 3) 3-weekly
   - Responses: 1.4%
   - n: 1

10. Carboplatin (AUC details in question 3) with **oral etoposide** (50 mg bd for 7 days) 4-weekly
    - Responses: 2.7%
    - n: 2

11. Carboplatin (AUC details in question 3) with **IV etoposide** (100 mg/m² IV for 3 days) 3-weekly
    - Responses: 20.6%
    - n: 15

12. Carboplatin (AUC details in question 3) with **IV etoposide** (120 mg/m² for 3 days) 3-weekly
    - Responses: 1.4%
    - n: 1

13. Carboplatin (AUC details in question 3) with **oral etoposide** (200 mg/m² on days 1, 2 and 3) 3-weekly
    - Responses: 5.5%
    - n: 4

14. Carboplatin (AUC details in question 3) with **IV etoposide** (100 mg/m² IV on day 1) followed by **oral etoposide** (200 mg/m² on days 2 and 3) 3-weekly
    - Responses: 10.9%
    - n: 8

15. Carboplatin (AUC details in question 3) with **IV etoposide** (120 mg/m² IV on day 1) followed by **oral etoposide** (200 mg/m² on days 2 and 3) 3-weekly
    - Responses: 4.1%
    - n: 3

16. I don’t know
    - Responses: 2.7%
    - n: 2

17. Other (please specify)
    - Responses: 5.5%
    - n: 4

*IV intravenous, bd twice a day, n number, % percentage—most common answers are highlighted*
LEADS FROM SMALL CELL LUNG CANCER

NCCN Guidelines Version 1.2019
Small Cell Lung Cancer

PRINCIPLES OF SYSTEMIC THERAPY*

Systemic therapy as primary or adjuvant therapy:
• Limited stage (maximum of 4–6 cycles):
  › Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3¹
  › Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3¹
  › Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3²
  › Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3³
  › During systemic therapy + RT, cisplatin/etoposide is recommended
     (category 1).
  › The use of myeloid growth factors is not recommended during
     concurrent systemic therapy plus radiotherapy (category 1 for not
     using GM-CSF).⁴

• Extensive stage (maximum of 4–6 cycles):
  › Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and
    atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by
    maintenance atezolizumab 1,200 mg (category 1, preferred)⁵,⁶
  › Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3¹,⁶
  › Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3¹,⁷
  › Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3¹,⁷
  › Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3¹,⁹
  › Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 2, 3¹,¹⁰
  › Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 2, 3¹,¹¹
  › Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8¹,¹²

Subsequent systemic therapy:²
• Clinical trial preferred.
  › Relapse ≤6 mo, PS 0-2:
    › Topotecan PO or IV¹³-¹⁵
    › Irinotecan¹⁵
    › Paclitaxel¹⁷,¹⁸
    › Docetaxel¹⁹
    › Temozolomide²⁰,²¹
    › Nivolumab ± ipilimumab²²,²³
    › Pembrolizumab²⁴
    › Vinorelbine²⁵,²⁶
    › Oral etoposide²⁷,²⁸
    › Gemcitabine²⁹,³⁰
    › Cyclophosphamide/doxorubicin/vincristine (CAV)¹²
    › Bendamustine (category 2B)³¹
  › Relapse >6 mo: original regimen³²,³³

Consider dose reduction or growth factor support for patients
with PS 2
There is no standard treatment beyond first-line etoposide/platinum-based chemotherapy in patients with progressive poorly differentiated extra-pulmonary NEC.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patients</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olsen et al 2014¹</td>
<td><strong>Topotecan</strong> monotherapy (heavily pre-treated)</td>
<td>N=22</td>
<td>2.1 months</td>
<td>3.2 months</td>
</tr>
<tr>
<td>Hadoux et al 2013²</td>
<td>Oxaliplatin-based chemotherapy (mostly 5-Fluorouracil [5-FU], leucovorin, and oxaliplatin [FOLFOX])</td>
<td>N=21</td>
<td>4.3 months</td>
<td>9.5 months (Longer with Ki-67&lt;55%)</td>
</tr>
<tr>
<td>Hentic et al 2012³</td>
<td>5-FU/leucovorin and irinotecan (<strong>FOLFIRI</strong>)</td>
<td>N=19</td>
<td>4 months</td>
<td>18 months (Date of diagnosis to death)</td>
</tr>
<tr>
<td>Olsen et al 2012⁴</td>
<td><strong>Temozolomide</strong> monotherapy</td>
<td>N=28</td>
<td>2.4 months</td>
<td>3.5 months</td>
</tr>
<tr>
<td>Welin et al 2011⁵</td>
<td><strong>Temozolomide</strong> monotherapy or in combination with capecitabine and some with bevacizumab</td>
<td>N=25</td>
<td>6 months</td>
<td>22 months</td>
</tr>
</tbody>
</table>

A multi-centre, randomised, parallel group, open-label, phase II, single-stage selection trial of liposomal irinotecan (nal-IRI) and 5-fluorouracil (5-FU)/folinic acid or docetaxel as second-line therapy in patients with progressive poorly differentiated extra-pulmonary neuroendocrine carcinoma (NEC) - NCT03837977

Eligible patients (N=102)
- Histologically-confirmed poorly differentiated extra-pulmonary NEC (G3)
- Prior treatment with first-line platinum-based chemotherapy
- ECOG performance status ≤2
- Radiological evidence of disease progression OR discontinuation of first-line platinum-based chemotherapy due to intolerance
- Tumour Ki-67 >20%

Arm A
Liposomal irinotecan (nal-IRI) 80mg/m² IV over 90 minutes, 5-FU (2400mg/m² over 46 hours), leucovorin (400mg/m² over 30 minutes) - Every 14 days

Arm B
Docetaxel 75mg/m² IV over 60 minutes Every 21 days

Treatment will continue until intolerable toxicity or progressive disease

(Computed Tomography every 8 weeks [± 7 days], Quality of life every 6 weeks)
LESSON OF THE MONTH…
Patients whose “unresectable disease” becomes resectable

Curative surgery after neoadjuvant chemotherapy in metastatic poorly differentiated neuroendocrine carcinoma

H. Sørbye, B. Westre, A. Horn

Figure 1. (a) Baseline; (b) after 2 cycles of chemotherapy.
DOES IMMUNOTHERAPY HAVE A ROLE?
PD-L1 expression in small cell neuroendocrine carcinomas

Anne M. Schultheis1,2, Andreas H. Scheel1, Luka Ozretić1,3, Julie George1,3, Roman K. Thomas1, Thorsten Hagemann4, Thomas Zander1,4, Jürgen Wolf1,5, Reinhard Buehler1,6

1 Institute of Pathology, University Hospital Cologne, Cologne, Germany
2 Department of Translational Genomics, University of Cologne, Cologne, Germany
3 Centre for Cancer and Inflammation, Barts Cancer Institute, Queen Mary University of London, London, UK
4 Center for Integrated Oncology (CIO), Cologne, Germany

Received 17 July 2014; revised 21 October 2014; accepted 11 December 2014

Human Pathology (2017) 48, 49–54

Original contribution

Expression of PD-1 and PD-L1 in poorly differentiated neuroendocrine carcinomas of the digestive system: a potential target for anti-PD-1/PD-L1 therapy

Jordan A. Roberts MD, Raul S. Gonzalez MD, Satya Das MD, Jordan Berlin MD, Chuanjun Shi MD, PhD

1Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN, 37232, USA
2Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, 14642, USA
3Department of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN, 37232, USA


• PD-L1 expression is associated with higher tumour grade (G3) in metastatic GEP-NETs
• Expression of PD-1 may be present on tumour cells as well as on tumour-associated immune cells
• 30% of patients with well-differentiated small bowel NETs expressed PD-L1 within tumour cells and/or TILs
PD-L1 INHIBITION IN MERKEL CELL

- Oncogenesis linked to Merkel cell polyomavirus integration and UV-induced mutations
- Phase II study of avelumab in post-chemo patients with stage IV Merkel cell carcinoma

Kaufman et al Lancet Oncol 2016;17:1374-1385
ASSESSMENT OF MUTATIONAL FREQUENCY

Somatic mutation frequencies in exomes from 3,083 tumour–normal pairs

ASSESSMENT OF MISMATCH REPAIR DEFICIENCY

“Neuroendocrine”
Well- or poorly differentiated?
G1, G2 or G3?
GEP? Lung? Other?

Le et al., Science 2017;357:409–413
PDR001 STUDY (SPARTALIZUMAB)
Best % Change From Baseline in Target Lesions

Thoracic cohort

| Decrease in best % change from baseline | 14 (48) |
| Increase in best % change from baseline | 15 (52) |

GI cohort

| Decrease in best % change from baseline | 8 (28) |
| Increase in best % change from baseline | 21 (72) |

Pancreatic cohort

| Decrease in best % change from baseline | 10 (32) |
| Increase in best % change from baseline | 21 (68) |

GEP NEC cohort

| Decrease in best % change from baseline | 1 (6) |
| Increase in best % change from baseline | 15 (94) |

Yao et al Ann Oncology 2018;29 (suppl 8):viii467-viii478
## SELECTION OF ONGOING STUDIES

<table>
<thead>
<tr>
<th>Phase</th>
<th>Checkpoint inhibitor</th>
<th>Indication</th>
<th>Registration</th>
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<tbody>
<tr>
<td>I</td>
<td>CK-301</td>
<td>Merkel</td>
<td>Australia</td>
</tr>
<tr>
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<td>NCT03212404</td>
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<tr>
<td>Ib</td>
<td>JS001</td>
<td>NET</td>
<td>China</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT03167853</td>
</tr>
<tr>
<td>I/II</td>
<td>Durvalumab + tremelimumab + Poly ICLC</td>
<td>Merkel</td>
<td>USA</td>
</tr>
<tr>
<td>II</td>
<td>Avelumab</td>
<td>Prostate NETs</td>
<td>USA</td>
</tr>
<tr>
<td>II</td>
<td>Nivolumab + ipilimumab</td>
<td>Rare cancers</td>
<td>Australia</td>
</tr>
<tr>
<td>II</td>
<td>Nivolumab + ipilimumab (adjuvant)</td>
<td>Merkel</td>
<td>Germany</td>
</tr>
<tr>
<td>II</td>
<td>PDR001</td>
<td>NETs and NECs (GEP and lung)</td>
<td>Global</td>
</tr>
<tr>
<td>II</td>
<td>Durvalumab</td>
<td>NEC, 2nd line</td>
<td>Spain</td>
</tr>
<tr>
<td>II</td>
<td>Pembrolizumab (Keynote 0028)</td>
<td>All NEN</td>
<td>Global</td>
</tr>
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</table>
HETEROGENEITY WITHIN HG-NECs
NOT ALL PATIENTS WITH G3-NEC ARE THE SAME

Differences in proliferation?

Nordic NEC study

<table>
<thead>
<tr>
<th>Ki67 &lt;55%</th>
<th>RR (%)</th>
<th>SD (%)</th>
<th>PFS (mo) Med (95%CI)</th>
<th>OS (mo) Med (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
<td>47</td>
<td>4 (3.2-4.8)</td>
<td>14 (10.7-17.3)</td>
</tr>
<tr>
<td>Ki67 ≥55%</td>
<td>42</td>
<td>24</td>
<td>4 (3.1-4.9)</td>
<td>10 (8.4-11.6)</td>
</tr>
</tbody>
</table>
NOT ALL PATIENTS WITH G3-NEC ARE THE SAME

Differences between small cell and large cell?

Netherlands Cancer Registry

<table>
<thead>
<tr>
<th>5-year Relative Survival</th>
<th>LC-NEC</th>
<th>SC-NEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>20%</td>
<td>6%</td>
</tr>
<tr>
<td>GI patients</td>
<td>32%</td>
<td>6%</td>
</tr>
<tr>
<td>Localised (GI)</td>
<td>61%</td>
<td>12%</td>
</tr>
<tr>
<td>Metastatic (GI)</td>
<td>18%</td>
<td>2%</td>
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</tbody>
</table>
NOT ALL PATIENTS WITH G3-NEC ARE THE SAME

Differences in NEC score?

Prognostic factors identified by log-rank test, Cox-regression, and logistic regression analyses (n=313)
Ki-67 immunostaining reveals intra-tumoral proliferative heterogeneity in a lymph node metastasis from a G1 ileal neuroendocrine tumour:
- G1 area in the upper half of the picture
- G3 area at the bottom
ANTICIPATING POTENTIAL PITFALLS

Recognition of heterogeneity | functional imaging

SSTRI ([68Ga]-DOTATATE) and FDG scan pair
- some lesions with spatially concordant FDG uptake (closed arrows)
- some sites of disease which are SSTRI-positive but FDG-negative (open arrows)
- no sites which are FDG-positive and SSTRI-negative

*With image display thresholds set at: $S_{\text{max}}(\text{SSTRI}) = 15$ $S_{\text{max}}(\text{FDG}) = 7$

ASSESSMENT IS DYNAMIC
Change in tumour behaviour over time

“After PD was observed, the therapeutic strategy was changed. Specifically, in the group of patients who reported a grade modification”
ASSESSMENT IS DYNAMIC
Change in tumour behaviour over time

Upstage in grade in 12 patients (6 siNET; 2 panNET; 3 bronchial; 1 rectum)
- 4 (25%) patients from G1 to G2
- 2 (13%) from G2 to G3
- 5 (31%) from G1 to G3

“...if tumor variability, and potentially dedifferentiation, is identified as a feature of NETs, the need for repeating biopsies over the course of disease may arise, especially when dealing with such a long natural history as that of NETs”

SUMMARY

In the management of patients with high-grade NECs

- Diagnosis depends on morphology and grade (Ki67)
- Staging involves cross-sectional (CT/MR) and functional (FDG-PET) imaging
- Platinum/etoposide chemotherapy is standard first-line
- There is no second-line “standard”; clinical trials are important
- The use of immunotherapy is investigational
- Need to consider heterogeneity
  - On pathology, laboratory tests or imaging…
  - …as a dynamic process over time
There is no standard treatment beyond first-line etoposide/platinum-based chemotherapy in patients with progressive poorly differentiated extra-pulmonary NEC.

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**Second-line treatment in patients (pts) with advanced extra-pulmonary poorly differentiated neuroendocrine carcinoma (EP-PD-NEC): a systematic review and meta-analysis**

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<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patient (N)</th>
<th>Progression-free survival (PFS)</th>
<th>Overall survival (OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olsen et al 2014⁴</td>
<td>Temozolomide monotherapy</td>
<td>N=28</td>
<td>2.4 months</td>
<td>3.5 months</td>
</tr>
<tr>
<td>Hentic et al 2012⁵</td>
<td>5-FU/leucovorin and irinotecan (FOLFIRI)</td>
<td>N=19</td>
<td>4 months</td>
<td>16 months</td>
</tr>
<tr>
<td>Hadoux et al 2013</td>
<td>Oxaliplatin-based chemotherapy (mostly 5-Fluorouracil [5-FU], leucovorin, and oxaliplatin [FOLFOX])</td>
<td>N=21</td>
<td>4.3 months (Longer with Ki-67&lt;55%)</td>
<td>9.5 months (Longer with Ki-67&lt;55%)</td>
</tr>
<tr>
<td>Olsen et al 2012³</td>
<td>Temozolomide monotherapy or in combination with capecitabine and some with bevacizumab</td>
<td>N=25</td>
<td>6 months</td>
<td>22 months</td>
</tr>
</tbody>
</table>

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ASSESSMENT OF MISMATCH REPAIR DEFICIENCY

- Phase 2 study of pembrolizumab (anti–PD-1)
- 41 patients with metastatic carcinoma with or without mismatch-repair deficiency
- Response Rate | CRC: 40% (4/10) MMR deficient; 0% (0/18) MMR proficient
  Non-CRC: 71% (5/7) MMR deficient

WES somatic mutations per tumour:
1782 MMR-deficient vs. 73 MMR-proficient tumours (p=0.007)
High mutational loads associated with prolonged PFS (p=0.02)