Consensus guidelines for high grade gastro-entero-pancreatic (GEP) neuroendocrine tumours and neuroendocrine carcinomas (NEC)

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Introduction

Neuroendocrine carcinomas (NEC) are rare in the gastrointestinal (GI) tract, whereas they are frequent in the form of small cell carcinoma (SCLC) in the lung. Therefore, most of the suggested guidelines arise from analogy to SCLC. As for other extra-pulmonary primary tumor locations, published data on NEC of the GI tract is scarce. This guideline encompasses all WHO grade 3 gastroenteropancreatic (GEP) neoplasms; however, in the future grade 3 neuroendocrine neoplasms will probably be separated according to differentiation, as explained below and potentially according to organ of origin such as for well differentiated NET G1/G2.

According to the WHO classification 2010, NEC are defined as poorly differentiated neuroendocrine neoplasms with Ki-67 >20% and hence of grade G3. Increasing evidence suggests that G3 neuroendocrine neoplasms are not a homogenous entity and can be further sub-classified into biologically relevant subgroups. A separation by proliferative index (Ki-67> 55%) was shown to have clinical implications regarding response to chemotherapy (CT) and prognosis: NEC with Ki-67 indexes >55% responded better to platinum-based CT and nevertheless had a 4 month shorter median survival than G3 NENs in the lower proliferative range (20%-55%) [1]. More recent publications show that morphological differentiation and Ki-67 is able to separate prognostic groups among the G3 group and therefore a separation of well differentiated NET G3 from poorly differentiated NEC G3 is emerging [2] [3] [4]. The exact criteria need to be defined both on the morphological and on the molecular level. The spectrum of mutations of well differentiated pancreatic NET is different from the spectrum of pancreatic NEC [5], suggesting different ways of tumorigenesis. However, to date there is no solid data that adequately address the implications of these observations in terms of treatment effect of the different available regimens.

Epidemiology

The gastroenteropancreatic tract is the most common site of extrapulmonary NEC, accounting for 35% to 55% of all NECs originating from the lung. Only about 5% of all gastrointestinal NEN have a Ki-67 > 20% [6, 7]. This frequency might differ by organ, with about 7% in the pancreas [7], and up to 40% in the colon [8]. GEP NEC are therefore very rare neoplasms representing less than 1% of all GI malignancies. Up to 85% have metastases at the time of diagnosis (65% distant) [1, 6]. Metastases are most frequently found in the liver (70%) followed by lung (15%), bone (15%) and brain (4%) [1]. There is no difference known between genders. The mean age at diagnosis is 60 years [1].
Clinico-pathological features

As the great majority of these tumours are not associated with a hormonal syndrome (<5%), and more than two thirds of patients present with advanced disease, clinical presentation is dominated by tumour-derived site-specific symptoms and the constitutional syndrome characteristic of advanced cancer (anorexia, weight loss, fatigue). Depending upon tumour location a wide variety of symptoms may occur. The neuroendocrine nature of these tumours is generally not suspected from the clinical presentation, although as in SCLC paraneoplastic syndromes may occur in some patients (i.e., Cushing or Inappropriate ADH Secretion Syndromes). A detailed anamnesis and physical examination are fundamental to appropriately guide diagnostic procedures.

According to the WHO 2010 classification NEC are poorly differentiated, highly aggressive neoplasms, sometimes with organoid features, marked nuclear atypia and multifocal necrosis [9]. A diffuse expression of neuroendocrine markers (diffuse for Synaptophysin, focal for Chromogranin-A, and the latter may be absent) separates the entity pathologically from poorly differentiated carcinoma.

The grading introduced by ENETS in 2006 [10] of neuroendocrine carcinomas is by definition G3, either based on a proliferation index >20% or more than 20 mitosis in 10/HPF. This proposition has been adopted by the WHO classification and was shown repeatedly to be clinically applicable in predicting a very aggressive subset of NEN [7].

Prognosis and survival

Survival is poor in NEC, ranging from 38 months for patients with localized disease to 5 months in the metastatic setting according to the SEER population registry data, that involved 2546 patients diagnosed with GI NEC from 1973 to 2012 in the USA[11]. Median survival in the metastatic setting may be as short as 1 month for patients receiving only best supportive care, up to 12-19 months for those treated with best available therapy [1, 12]. Only 5% of patients are long time survivors [7]. Progression free survival after cisplatin-based CT and overall survival differs according to location of the primary tumor, with poorer reported outcomes in esophageal, colonic and rectal NECs compared to gastric and pancreatic ones in some large European series [1]. Survival of pancreatic NECs was in contrast poorer in Japanese patients [13]. Poor performance status, high proliferation rate, elevated baseline lactate dehydrogenase and thrombocytosis are other factors that have been also associated with a worse prognosis.
Diagnostic Procedures

Biochemical Tests
Plasma Chromogranin A may be elevated in up to two thirds of patients with advanced NECs [1], although levels are generally lower than those observed in well differentiated tumours [14] [15]. In contrast, the levels of other tumour markers such as neuron-specific enolase (NSE) are higher in poorly differentiated tumours than in NETs, and are significantly associated with survival. However, the role of circulating tumor markers to predict and monitor outcome has not been properly assessed in extra-pulmonary NECs. Screening for other hormonal markers is not justified unless clinically indicated.

Endoscopic and Imaging Procedures
Endoscopic examination of the primary tumour site is recommended, which is also useful to obtain a biopsy for histological diagnosis. If this is not feasible, endoscopic ultrasound-guided or percutaneous procedures can be useful. Once the histological diagnosis of a NEC G3 has been confirmed, complete staging using whole body CT scan or MRI should be performed to assess the extent of disease and to design the most appropriate therapeutic strategy. A lung primary shall be reasonably excluded (negative imaging studies of the lung). FDG-PET may be useful if radical surgery is being pursued or if clarification of equivocal findings on conventional imaging may change the therapeutic approach. Radiolabelled somatostatin analogue scans are not routinely recommended as poorly differentiated tumours generally do not express somatostatin receptors. However, data from large series indicate positive SRI findings in a substantial proportion of patients with certain primary tumours (up to 45% of pancreatic NECs), particularly those with proliferative indexes in the low range of G3, and may differ by histological subtype (45% of small cell versus 32% of large cell NECs) [1]. In the absence of neurologic symptoms, brain CT or MRI are not recommended, as the incidence of brain metastasis in extra-pulmonary NECs is rather low (<5%) [1]. Bone scans are neither indicated if there is no clinical or biochemical suspicion of bone metastasis. In the presence of elevated lactate dehydrogenase (LDH), peripheral blood leukoerythroblastosis or thrombocytopenia, a bone marrow biopsy may be considered.

Minimal consensus statement
Clinical signs and symptoms shall guide the appropriate diagnostic procedures. Chromogranin A and NSE testing is not mandatory although they may be useful if elevated at diagnosis. Proper assessment of their utility in extra-pulmonary NECs is, however, pending. Other hormone tests are not routinely recommended.

A minimal diagnostic workup should include site-specific endoscopic assessment with tumour biopsy, and whole body CT scan (and/or MRI) for tumour staging. In patients with
metastatic disease, ultrasound-guided percutaneous biopsy may be performed if feasible. Somatostatin receptor scintigraphy is not routinely indicated but may be considered in tumours with proliferative indexes in the low range of G3 (Ki-67 <55%). Bone scans or brain imaging (CT or MRI) shall not be performed in the absence of site-specific symptoms. FDG-PET may be considered in patients in whom radical surgery is being pursued or if clarification of equivocal findings on conventional imaging may change the therapeutic approach. FDG-PET may be useful in resectable cases for whole body assessment.

Histopathology and Genetics of pdNEC

Histopathologically, NEC show a neuroendocrine phenotype by immunohistochemistry, in large cell NEC a positivity for synaptophysin is mandatory, chromogranin-A staining is variable and may be weak or absent. Negativity of both markers might occur rarely in small cell NEC (<5% [1]). Other neuroendocrine markers such as NSE or CD56 are less specific and must be used with caution. Ki-67 is by definition >20% [10] and in half the cases is > 55% [1]. Punctate or geographic necrosis is frequent. Reporting of the above immunohistochemical results as well as the proliferative index by mitosis is essential. Somatostatin receptor 2A (Sstr 2a) immunohistochemistry is optional [16, 17]. Over 90% of G3 NEC do not show production of hormones [17].

In the setting of a carcinoma of unknown primary, the expression of transcription factors such as Ttf1, Cdx-1 or Isl1 cannot be used to help localize the site of the primary tumor [18].

Care must be taken to differentiate NEC from poorly differentiated adenocarcinoma, especially in certain organs such as the pancreas, were differential diagnosis with acinic cell carcinoma might be particularly challenging [19]. NEC are separated into large cell and small cell types, however no clear clinicopathological differences between the two types have been shown for the pancreas [19].

Pancreatic NEC show a genetic profile different from NET with frequent mutations in p53 and RB [5] and a much higher mutation rate (in review), similar to pulmonary small cell carcinoma. Furthermore, up to 40% of NECs present a minor component of adenocarcinoma (colon, [20], stomach [21]) or squamous cell carcinoma (esophagus, anus). If the non-endocrine component exceeds 30%, the neoplasms is classified as mixed adenoneuroendocrine carcinoma (MANEC). Differentiation, together with proliferation and mutation spectrum will be important in discriminating NET G3 from NEC G3 in the future [2] [3] [4].
**Minimal consensus statement**

Routine pathology report should include morphology (large-cell vs small-cell and differentiation), staining for CgA and synaptophysin and Ki-67 estimate or/and mitotic count.

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**Treatment**

Evidence to support treatment recommendations for gastroenteropancreatic NEC G3 is scarce and derives from limited retrospective series and very few small non-controlled clinical trials. Most investigators, therefore, treat this entity in analogy to the much more common SCLC due to their histological and clinical resemblance. Bearing these caveats in mind, guidance is hereby provided. Nevertheless, generating prospective and preferably controlled data is greatly needed and encouraged in this setting.

**Surgery**

Curative surgery is usually attempted in localized disease, although retrospective series indicate that as a sole therapeutic modality it is rarely curative [22]. Given the high relapse rate observed following radical surgery, most clinicians would advocate platinum-based adjuvant therapy in this setting. Data reported by Casas et al of a large series of oesophageal small cell carcinomas support this approach [23]. In this study, survival was 20 months for patients who received systemic chemotherapy in addition to local treatment versus only 5 months for those who were treated with local therapy only, and the type of treatment was found to be an independent prognostic factor in multivariate analysis. Some authors propose neoadjuvant chemotherapy followed by definitive surgery, although data to support this approach is scarce [24]. In patients with important comorbidities or in anatomical sites where surgical resection is not advisable due to its high morbidity (i.e., esophagus), a definitive course of radiotherapy and chemotherapy is a reasonable treatment strategy. In the context of advanced metastatic disease, debulking or cytoreductive surgery and surgical resection of metastasis are not recommended. Other ablative strategies of liver metastasis (i.e., radiofrequency ablation, TACE) are also discouraged.

**Medical therapy**

Chemotherapy is an essential part of the multimodality approach for localized NECs and the mainstay of care in advanced disease. Survival of patients with metastatic NECs treated with chemotherapy is widely variable (from 7 to 19 months) but suggests a substantial improvement over that reported for patients that receive only best supportive care (1 month). No randomized studies, however, have properly addressed the magnitude of this effect. Rapid referral for consideration of palliative chemotherapy is recommended as rapid...
performance status deterioration may occur and preclude further therapy. Based on its established role in metastatic SCLC, cisplatin and etoposide (EP) has been one of the most widely used regimens in GEP-NECs (Table 1) [25] [26] [27] [28] [29] [1] [13], with response rates in the largest recent series of ~ 30% and median survival of around one year. In one of the largest series published to date, Sorbye et al observed that Ki-67 was significantly associated with response to chemotherapy. Indeed, patients with Ki-67 values > 55% had greater response rate (42% versus 15%) although poorer survival (10 vs 14 months) than patients with Ki-67 <55%. Other negative prognostic factors in this study were poor performance status, primary colorectal tumors and elevated platelets or lactate dehydrogenase (LDH) levels, which were all associated with decreased survival.

Alternative regimens substituting carboplatin for cisplatin, or irinotecan for etoposide, have been validated in SCLC and seem at least equivalent in terms of efficacy in limited series of GEP-NECs (Table 1) [30] [31] [32] [33] [34] [13, 35], with different toxicity profiles. In the context of advanced stage SCLC, a randomized study conducted in Japan demonstrated that the combination of irinotecan and cisplatin (IP) was associated with improved overall survival as compared to the standard cisplatin and etoposide combination [36]. Two subsequent randomized western trials, however, failed to confirm this superiority. Both regimens produced comparable efficacy, with less hematologic and greater gastrointestinal toxicity with the irinotecan combination (particularly diarrhea and vomiting) [37] [38]. Consistent with these findings, large retrospective data of systemic chemotherapy for advanced GEP-NECs from 23 Japanese institutions documented the IP regimen was associated with greater response rates (50% vs 28%) and survival (13 vs 7 months) than the EP regimen, and this difference was more remarkable in hepatobiliarypancreatic NECs. Prognostic factors in this study included primary tumor site (being hepatobiliarypancreatic primaries the ones with the worst prognosis) and elevated baseline LDH levels, whereas treatment schedule was not an independent predictive factor for survival. Three-drug regimens such as cisplatin, etoposide and paclitaxel do not seem to substantially improve efficacy and are significantly more toxic [39].

Evidence for salvage therapy in patients progressing one first-line platinum-based regimens is very limited (Table 1) [40] [41] [42] [43] [44] [13] [1]. Overall, response rates are lower (18% in the NORDIC NEC study), although small series have documented response rates of 23% to 40% with oxaliplatin-based (XELOX, FOLFOX) or irinotecan-based (FOLFIRI, IP) regimens. Welin et al reported a 33% response rate with temozolomide, alone or in combination with capecitabine and bevacizumab, in a cohort of 25 patients with poorly differentiated NECs (17 of GEP origin) [43]. A Ki-67 index < 60% was predictive for response to treatment and survival. In contrast, no responses were observed in another series of 28 NECs treated with temozolomide monotherapy [44]. Retreatment with platinum/etoposide...
may also be considered in patients that achieved good durable responses upfront and have progressed after a treatment break of at least 3 months, provided no cumulative toxicity (i.e., neurotoxicity, ototoxicity) precludes further treatment with platinum agents. Other agents tested include amrubicin, S-1 or taxanes (Table 1).

Other treatment options (Radiotherapy, PRRT)
In contrast to recommendations for patients with limited-stage SCLC, prophylactic cranial irradiation is not indicated in patients with successfully treated localized GEP NECs, as the incidence of brain metastasis in patients with extra-pulmonary NECs is rather low. Palliative radiotherapy may be considered for localized bone metastasis to control pain or to prevent skeletal complications.

Although a subgroup of NECs do express somatostatin receptors, there are no data to support the use of somatostatin analogs in this context. Some case reports have communicated long-lasting responses to peptide receptor radionucleotide therapy (PRRT) in NECs with high expression of somatostatin receptors, but this therapeutic strategy is generally not successful in the majority of G3 tumors [45].

Minimal consensus statement on treatment
For patients with localized disease, combination of platinum-based chemotherapy with local treatment consisting of surgery, radiotherapy or both probably offers the greatest likelihood of long-term survival. Debulking or surgical resection of metastasis are not recommended. Systemic chemotherapy is indicated in advanced inoperable disease, provided the patient has adequate organ function and performance status and patients should be rapidly referred for consideration of palliative chemotherapy. The combination of cisplatin and etoposide, or alternative regimens substituting carboplatin for cisplatin, or irinotecan for etoposide, are recommended as first-line therapy. Since response rates of these regimens are lower in patients with Ki-67 in the lower range of G3 (20-55%), other treatment options may be explored in these patients (especially perhaps for NEC of GI origin). While 2nd-line regimens have not been evaluated rigorously, options include temozolomide-, irinotecan- or oxaliplatin-based schedules as main alternatives. There are no data to support the use of somatostatin analogs or PRRT in patients with GEP NECs expressing somatostatin receptors. Prophylactic cranial irradiation is not indicated in patients with limited-stage disease in complete remission.

Follow-up
Follow-up recommendations are based on expert opinion as there is no solid evidence to support the type and frequency of performance of specific procedures. Patients with
Localized G3 NECs who have undergone complete resection are recommended to be followed every 3-6 months during the first 2-3 years following surgery, and then every 6-12 months up to 5 years. Conventional imaging (CT scan or MRI) should be performed in these follow-up visits, but general tumor markers (i.e., chromogranin A or neuron-specific enolase) are only indicated if elevated at diagnosis. Somatostatin receptor imaging procedures are generally not warranted in this setting, particularly if negative at diagnosis. FDG-PET may be indicated if equivocal findings are encountered on conventional imaging and/or if salvage surgery is being considered.

Follow-up of patients with advanced disease shall be customized depending upon tumor kinetics (Ki-67 proliferative index and actual growth rate documented by serial CT scans), treatment strategy, side effects of therapy and general health condition. Clinical assessment visits shall be scheduled frequently, as these patients generally present fast tumor kinetics, are highly symptomatic and/or receive toxic agents. Clinical judgement is advised to establish the appropriate assessment interval. Conventional imaging procedures are recommended to be performed every 2-3 months while on active therapy.

**Minimal consensus statement**

*In patients with localized R0/R1 resected NEC G3, conventional imaging (CT and/or MRI) and assessment of circulating tumor markers (if elevated at baseline) are recommended to be performed every 3 months during the first 2-3 years after surgical resection, and every 6-12 months up to 5 years following surgery. In patients with advanced disease NEC G3, frequent clinical assessment visits shall be performed and conventional imaging is recommended every 2-3 months while on active therapy.*

Please also refer to consensus guideline updates for other gastro-entero-pancreatic (GEP) neuroendocrine tumours [46-51, this issue].
References


18. Agaimy, A., et al., ISL1 expression is not restricted to pancreatic well-differentiated neuroendocrine neoplasms, but is also commonly found in well and poorly differentiated neuroendocrine neoplasms of extrapancreatic origin. Modern Pathology, 2013. 26(7): p. 995-1003.


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Fig. 1 Diagnostic algorithm for neuroendocrine carcinoma and G3 tumours.
Fig. 2 Therapeutic algorithm for neuroendocrine carcinoma and G3 tumours
Table 1. Series of patients with advanced NEC G3 of the GI tract treated with chemotherapy

<table>
<thead>
<tr>
<th>First author</th>
<th>No of patients</th>
<th>Primary site</th>
<th>CT regimen</th>
<th>RR</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST LINE THERAPY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moertel</td>
<td>18</td>
<td>GEP (14), lung (1), UKP (3)</td>
<td>Cisplatin/Etoposide</td>
<td>67%</td>
<td>19 months</td>
</tr>
<tr>
<td>Mitry</td>
<td>41</td>
<td>GEP (20), lung (10), H&amp;N (4),</td>
<td>Cisplatin/Etoposide</td>
<td>42%</td>
<td>15 months</td>
</tr>
<tr>
<td>Deutshein</td>
<td>18</td>
<td>UKP (7)</td>
<td>Cisplatin/Etoposide +/- Paclitaxel</td>
<td>17%</td>
<td>NR</td>
</tr>
<tr>
<td>Iwasa</td>
<td>21</td>
<td>G3 NEC (primary NR)</td>
<td>Cisplatin/Etoposide</td>
<td>14%</td>
<td>6 months</td>
</tr>
<tr>
<td>Patta</td>
<td>8</td>
<td>Hepatobiliary &amp; Pancreas</td>
<td>Cisplatin/Etoposide</td>
<td>63%</td>
<td>10 months</td>
</tr>
<tr>
<td>Sorbye</td>
<td>252</td>
<td>Colorectal</td>
<td>Cisplatin/Etoposide</td>
<td>31%</td>
<td>12 months</td>
</tr>
<tr>
<td>- 129</td>
<td>GEP (69%), UKP (31%)</td>
<td>Carboplatin/Etoposide</td>
<td>30%</td>
<td>11 months</td>
<td></td>
</tr>
<tr>
<td>- 67</td>
<td>Hainsworth</td>
<td>Paclitaxel/Carboplatin/Etoposide</td>
<td>53%</td>
<td>15 months</td>
<td></td>
</tr>
<tr>
<td>Ramella</td>
<td>27</td>
<td>GEP (15), lung (7), skin (4), other (4), UKP (48)</td>
<td>Platinum/Irinotecan</td>
<td>46%</td>
<td>12 months</td>
</tr>
<tr>
<td>Okita</td>
<td>12</td>
<td>GEP (18), H&amp;N (1), GU (1),</td>
<td>Cisplatin/Irinotecan</td>
<td>75%</td>
<td>23 months</td>
</tr>
<tr>
<td>Nakano</td>
<td>35</td>
<td>UKP (7)</td>
<td>Cisplatin/Irinotecan</td>
<td>64%</td>
<td>NR</td>
</tr>
<tr>
<td>Okuma</td>
<td>12</td>
<td>Gastric</td>
<td>Cisplatin/Irinotecan</td>
<td>50%</td>
<td>13 months</td>
</tr>
<tr>
<td>Lu</td>
<td>16</td>
<td>GEP (9), H&amp;N (18), GU/GYN</td>
<td>Cisplatin/Irinotecan</td>
<td>57%</td>
<td>11 months</td>
</tr>
<tr>
<td>Kulke</td>
<td>4</td>
<td>(5), UKP (12)</td>
<td>Cisplatin/Irinotecan</td>
<td>25%</td>
<td>NR</td>
</tr>
<tr>
<td>Yamaguchi</td>
<td>258</td>
<td>Esophagus</td>
<td>Cisplatin/Irinotecan</td>
<td>50%</td>
<td>13 months</td>
</tr>
<tr>
<td>- 160</td>
<td>GEP</td>
<td>Cisplatin/Etoposide</td>
<td>28%</td>
<td>7 months</td>
<td></td>
</tr>
<tr>
<td>- 46</td>
<td>GEP/UKP</td>
<td>GEP NEC/MANEC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SECOND OR THIRD LINE THERAPY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hentic</td>
<td>19</td>
<td>GEP</td>
<td>FOLFIRI</td>
<td>31%</td>
<td>18 months</td>
</tr>
<tr>
<td>Welin</td>
<td>25</td>
<td>GEP (17), UKP (5), lung (3)</td>
<td>TMZ +/- Capecitabine +/- Beva</td>
<td>33%</td>
<td>22 months</td>
</tr>
<tr>
<td>Olsen</td>
<td>28</td>
<td>GEP (18), UKP (6), lung (1),</td>
<td>TMZ</td>
<td>0%</td>
<td>4 months</td>
</tr>
<tr>
<td>Bajetta</td>
<td>13</td>
<td>GU (3)</td>
<td>XELOX</td>
<td>23%</td>
<td>NR</td>
</tr>
<tr>
<td>Ferrarotto</td>
<td>9</td>
<td>GEP (58%)</td>
<td>XELOX</td>
<td>29%</td>
<td>NR</td>
</tr>
<tr>
<td>Hadoux</td>
<td>20</td>
<td>GEP (75%)</td>
<td>FOLFOX</td>
<td>29%</td>
<td>10 months</td>
</tr>
<tr>
<td>Yamaguchi</td>
<td>25</td>
<td>G3 NEC (primary NR)</td>
<td>Amrubicin</td>
<td>4%</td>
<td>8 months</td>
</tr>
<tr>
<td>- 23</td>
<td>GEP NEC/MANEC</td>
<td>Platinum/Etoposide</td>
<td>17%</td>
<td>5 months</td>
<td></td>
</tr>
<tr>
<td>- 21</td>
<td>GEP NEC/MANEC</td>
<td>Irinotecan</td>
<td>5%</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>- 11</td>
<td>GEP NEC/MANEC</td>
<td>S-1</td>
<td>27%</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>- 5</td>
<td>GEP NEC/MANEC</td>
<td>Cisplatin/Irinotecan</td>
<td>40%</td>
<td>9 months</td>
<td></td>
</tr>
<tr>
<td>Sorbye</td>
<td>100</td>
<td>GEP NEC/MANEC</td>
<td>Various (Taxane-22; Tmz-35)</td>
<td>18%</td>
<td>19 months</td>
</tr>
</tbody>
</table>

Beva: bevacizumab; CT: chemotherapy; GEP: gastroenteropancreatic; GU: genitourinary; GYN: gynaecological; No: number; NR: not reported; RR: response rate; TMZ: temozolomide; UKP: unknown primary