Abstract
Neuroendocrine neoplasms (NENs) comprise a heterogeneous group of tumours, which can be classified into neuroendocrine tumours (NETs), neuroendocrine carcinomas (NECs) and mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs). To date, there is no consensus regarding the optimal therapy, which usually depends on the primary location and classification, according to morphological features of differentiation and proliferation rates. Nevertheless, multidisciplinary strategies combining medical treatments and locoregional strategies have yielded better efficacy results. Here, we report the case of a patient diagnosed with a nonfunctional rectal NECs with metastatic widespread to pelvic lymph nodes and bilateral lung metastases. The patient received three cycles of platinum-etoposide, concomitantly with palliative radiotherapy. Although CT scan after three cycles showed a significant partial response, there was an early fatal progression only 3 months after having stopped systemic therapy. As formerly described in the literature, this case highlights the aggressive behaviour of NECs, rare tumours that often present in advanced stages at diagnosis.

Introduction
Neuroendocrine neoplasms (NENs) are a heterogeneous family, including a wide range of malignancies derived from the diffuse endocrine system cells. NENs differ from adenocarcinomas in their cell of origin, as they arise from enterochromaffin cells distributed across a diversity of tissues. NENs are commonly classified according to their embryological and anatomical site of origin, proliferation index (immunohistochemistry for Ki-67) and their ability to secrete bioactive peptides (functional versus nonfunctional). International efforts led by the World Health Organization (WHO) and the European Neuroendocrine Tumour Society (ENETS) have lately established a specific standard classification. Based on morphologic, proliferation and biologic features, this prognostic classification aims to better tailor the type of tumour with optimal therapeutic strategies for these patients. Within this classification, NENs are mainly subdivided into well-differentiated (WD) and poorly differentiated (PD) NENs.

WD-NENs comprise neuroendocrine tumours (NET) G1, with mitosis <2/10 high-power field (HPF) and Ki-67 index ≤2%, and NET G2, with mitosis 2-20/10 HPF and Ki-67 index 3–20%. Histologically, they usually present without necrosis, with a cytoplasm enriched with secretory granules, which are
stained for neuroendocrine markers. NET G1 and G2 are usually asymptomatic slow-growing neoplasms, with a more indolent course, which can present characteristic hormone-producing patterns (e.g. insulinoma for insulin-secreting tumours\(^4\)). A third subclass of tumours, NET G3, fit also within the WD-NETs although they present higher mitosis >20 HPF and Ki-67 index >20%. NET G3 can still retain molecular aspects of WD-NENs (e.g. lower level of genomic instability and possibility of functioning products).\(^7\)

Surgery and locoregional therapies are the best treatments whenever feasible for WD-NETs.\(^8\) Unfortunately, more than 50% of NETs are diagnosed with advanced unresectable disease. Systemic chemotherapy has been historically regarded as the first-line option for rapidly progressive symptomatic WD-NETs. Streptozocin with fluoroprimidines, temozolamide or doxorubicin have been the preferred regimens, achieving overall response rates of 6–69%.\(^9\)–\(^12\) However, the widespread expression of somatostatin receptors amongst WD-NETs has enabled the use of somatostatin–receptor gamma scans for accurate staging,\(^13\) providing the rationale for the development of peptide receptor-targeted radionuclide therapy.\(^14\) Furthermore, somatostatin analogues such as lanreotide\(^15\) and octreotide\(^16\) have shown a significant improvement in progression-free survival (PFS) rates amongst WD-NET patients. Also, a better understanding of WD-NET molecular biology has led to the development of new targeted therapies. WD-NETs are highly vascularized tumours that express vascular endothelial growth factor and its receptor (VEGF/VEGFR).\(^17\) In 2011, 37.5 mg daily of sunitinib, a multitargeted tyrosine kinase inhibitor reported improved efficacy compared to placebo in advanced WD-pancreatic NETs (mPFS 11.4 versus 5.5 months, the hazard ratio (HR) 0.42; 95% confidence interval (CI): 0.26–0.66; p<0.001).\(^18\) The mammalian target of rapamycin (mTOR) is an intracellular kinase that plays a crucial role as a central regulator of growth, proliferation, cellular metabolism and angiogenesis and has been implicated in the molecular pathogenesis of NETs.\(^19\) The RADIANT-3 study showed that 10 mg of daily oral mTOR inhibitor everolimus, improved PFS amongst patients with pancreatic NET G1-2 compared with placebo (mPFS 11 versus 4.6 months, HR 0.35; 95% CI: 0.27–0.45; p<0.001).\(^20\) The RADIANT-4 study provided additional efficacy data of everolimus in a broadened population of advanced nonfunctional progressive WD-NETs of lung or any gastro-entero-pancreatic (GEP) origin.\(^21\)

Treatment for advanced NET G3 is not yet standardized, considering chemotherapy as the gold standard, particularly if the aim is a secondary surgery. Primary tumour removal and surgical debulking of hepatic metastases can reduce the symptoms and improve the pharmacological management and quality of life of these patients.\(^22\) The preferred systemic regimen in NET G3 should be in line with that implemented in NET G1-2 with Ki-67 index under 55%, whilst it might be appropriate to switch in line with that implemented in PD-NENs when Ki-67 is above 55%.\(^23\) PD-NENs encompass a subgroup of tumours whose molecular aspects resemble the carcinoma counterpart. PD-NENs or neuroendocrine carcinomas (NECs) enclose a heterogeneous group of high-grade neuroendocrine tumours that display neuroendocrine traits coexisting with a high-grade neuroendocrine component, usually progressing soon to standard treatment. In this context, the accurate pathological diagnosis and classification is crucial when facing a newly diagnosed rectal NECs, thus its clinical expression, prognosis and optimized therapeutic approach will significantly differ depending on the subtypes.\(^36\) Figure 1 proposes a diagnostic algorithm for rectal tumours.\(^37\)

Here, we present a case report of a rectal NECs, a very rare entity, focusing on a multidisciplinary treatment approach. We emphasize on a combined treatment with palliative chemotherapy and radiotherapy, depicting further molecular considerations that could help in delineating new therapeutic strategies beyond progression to standard treatment.
Case report

Written informed consent was obtained from the patient for publication of this report. A 76-year-old female presented with a 1-year history of rectal pain with intermittent bleeding and progressive constipation. A colonoscopy revealed an ulcerative lesion with irregular edges and infiltrative macroscopic aspect, located within the rectal ampulla, partially obstructing the descending colon; proximal to this lesion, there was bowel protrusion suggesting an extrinsic compression. During a colonoscopy, superficial biopsies were taken which showed undifferentiated small cells on the haematoxylin and eosin morphological staining. Further immunohistochemistry evaluation was positive for the neuroendocrine marker synaptophysin, together with the epithelial marker cytokeratin CAM 5.2, with a high Ki-67 index >80%. The negative CDX2 staining indicated that the tumoral cells had barely intestinal differentiation, therefore supporting the final diagnosis of an infiltrating highly undifferentiated SCNEC of the rectum38 (Figure 2).

The complete staging was performed with pelvic magnetic resonance imaging (MRI), which revealed the extension of the primary rectal tumour through the colon wall, infiltrating the posterior wall of the vagina together with radiological metastases to pelvic lymph nodes. A computed tomography (CT) scan of the chest, abdomen and pelvis confirmed distant bilateral lung metastases. Tumour markers, cancer antigen 125 (CA125), 19.9 (CA19.9) and serum chromogranin A were negative, whilst carcinoembryonic antigen (CEA) was slightly elevated at...
7.57 ng/ml (range 0–5 ng/ml). Twenty-four-hour urinary excretion of 5-hydroxyindoleacetic (5-HIAA) was normal. At her baseline assessment, the patient presented an Eastern Cooperative Oncology Group (ECOG) performance status of 1, due to worsened general condition related to her primary bulky tumour symptoms.

The case was discussed at our Colorectal Tumours Multidisciplinary Team Meeting, and it was deemed a cT4N2aM1 stage IV nonfunctioning rectal SCNEC, being considered for systemic chemotherapy without delay. The patient agreed to start palliative therapy, and upfront treatment with platinum-based chemotherapy was proposed (cisplatin 100 mg/m$^2$ iv. and etoposide 100 mg/m$^2$ iv. on day 1 of each cycle, with subsequent etoposide 200 mg/m$^2$ po. on days 2–3, every 21 days). Given the fact that lower gastrointestinal symptoms were difficult to control with optimized analgesia, external beam radiotherapy was prescribed and administered concomitantly with the first cycle of chemotherapy. Radiotherapy was well tolerated, achieving local clinical response only 3 weeks after completing the scheduled dose, with resolution of rectal pain and bleeding. However, the patient was able to receive only three cycles of the preplanned cisplatin and etoposide chemotherapy, due to the significant gastrointestinal and haematological toxicity that she presented, even despite frequent dose reductions and treatment delays. Her first evaluation CT scan showed an overall partial response, with the disappearance of bilateral lung nodules and significant shrinkage of primary rectal tumour and pelvic lymph nodes (Figure 3C). Given the impossibility of maintaining an optimal dose of chemotherapy in an elderly patient, and considering the maximum response achieved, it was agreed with the patient withholding the systemic therapy and start a close surveillance.

Unfortunately, a follow-up CT scan only 3 months after showed new progression of the lung and primary rectal tumours, and new multiple liver metastases. The formalin-fixed paraffin-embedded (FFPE) tissue specimen of the primary tumour underwent molecular profiling using next-generation sequencing techniques (customized panels for mutations with AmpliconSeq -Illumina®, and potential gene fusions with Nanostring -nCounter®) (Table 1). However, no relevant targetable alterations were found, and the patient rapidly presented clinical deterioration that urged hospitalization, which precluded the initiation of second-line palliative chemotherapy. The patient died 9 months after the initial diagnosis.
**Multidisciplinary therapeutic approach of NECs**

Considering their aggressive behaviour, newly diagnosed NECs must follow a multidisciplinary approach. If a patient is diagnosed with early-stage disease, upfront surgery should be offered. However, if it is not clear whether surgery is of benefit, especially taking into consideration the anatomical site of the primary and the high risk of systemic recurrences, there is also evidence of long-term survival from selected cases that received definitive chemoradiotherapy (e.g. oesophageal NEC). Nevertheless, there is a general consensus that surgery has to be considered only in cases of the locoregional disease, with a benefit seen of 64.5% 2-year OS. If resection is performed, it seems that patients who receive neoadjuvant or adjuvant therapy benefit the most, suggesting that micrometastases might contribute to poor surgical outcomes amongst limited-stage NECs.

A retrospective review led by Modrek and colleagues in 2015 established that radiotherapy significantly improved the prognosis in the setting of locoregional rectal NECs. The addition of concomitant radiotherapy reported local clinical response and improvement of survival, with 1-year OS of 71.1 versus 37.8% for the nonradiotherapy group. The currently available data suggest that there is no standard treatment regarding the optimal dose/fraction of radiotherapy for rectal NECs. The most frequent schedules are those in between 25 and 50 Gy, probably based on historical studies performed with cT3 or N positive rectal adenocarcinomas, or instead following the Swedish scheme – termed short-course radiotherapy or SCRT – for fragile patients, administrating 25 Gy in 5 Gy daily fractions. Both options have shown a good safety profile and high rates of local disease control. VMAT, a form of intensity-modulated radiotherapy (IMRT), greatly improved the conformation of the dose to a three-dimensional shape compared to conventional radiotherapy, thus achieving higher doses over tumour areas. The use of this technique drastically reduced acute and chronic toxicities, whilst improved local control. Guererro Urbano and colleagues compared several IMRT plans with conventional radiotherapy and reported grade 3-4 bowel toxicities in only 5% of the patients treated up to 50 Gy with pelvic doses. The radiotherapy scheme used in our patient was the short-course radiotherapy, which after its first publication in 2001 by the Swedish group, was compared to a normofractionated scheme, reporting no differences neither in overall survival nor in local control or toxicities. In contrast to small-
Table 1. Prescreening analysis by customized next-generation sequencing panels.

| AmpliconSeq mutation panel - Illumina®- |  |
|----------------------------------------|--|
| ABL1                                   | FLT3  |
| AKT1                                   | GATA1 |
| AKT2                                   | GNA11 |
| AKT3                                   | GNAQ  |
| ALK                                    | GNAS  |
| APC                                    | HRAS  |
| BRAF                                   | IDH1  |
| CDH1                                   | IDH2  |
| CDKN2A                                 | JAK1  |
| CSF1R                                  | JAK3  |
| CTNNB1                                 | KIT   |
| EGFR                                   | KRAS  |
| ERBB2                                  | MAG   |
| ERBB3                                  | MAP2K1|
| ESR1                                   | MET   |
| FBXW7                                   | MLH1  |
| FGFR1                                  | MPL   |
| FGFR2                                  | MSH6  |
| FGFR3                                  | MYC   |
| FGFR4                                   | NF2   |

| NanoString gene fusion panel - nCounter®- |  |
|----------------------------------------|--|
| EML4 E13-ALK E20                       | CD44 E1-FGFR2 E3 |
| EML4 E20-ALK E20                       | SLC45A3 E1-FGFR2 E2 |
| EML4 E6-ALK E20                        | FGFR3 E17-AES E2 |
| AKAP9 E8-BRAF E9                       | FGFR3 E17-ELAVL3 E2 |
| KIAA1549 E15-BRAF E9                  | FGFR3 E17-LETM1 intron10 |
| KIAA1549 E14-BRAF E9                  | FGFR3 E17 intron-TACC3 E4 |
| KIAA1549 E15-BRAF E11                  | FGFR3 E17-BAIAP2L1 E2 |
| BAG4 E2-FGFR1 E6                       | FGFR3 E17-TACC3 E4 |
| ERLIN2 E10-FGFR1 E4                    | FGFR3 E17-TACC3 E8 |
| FGFR1 E17-TACC1 E7                     | FGFR3 E17-TACC3 E10 |
| FGFR2 E17-AFF3 E8                      | FGFR3 E17-TACC3 E11 |
| FGFR2 E17-AHCYL1 E2                    | RANBP17 E28-FGFR3 E1 |
| FGFR2 E17-AE1 E12                      | EGFR vIII (E1-E8) |
| FGFR2 E17-BICC1 E3                     | MET E13-E15 |
| FGFR2 E17-CASP7 E4                     | LMNA E2- NTRK1 E10 |
| FGFR2 E17-CCDC47 E2                    | LMNA E2- NTRK1 E11 |
| FGFR2 E17-CIT E23                      | LMNA E10- NTRK1 E12 |
| FGFR2 E17-FAM76A E2                    | LMNA E10- NTRK1 E13 |
| FGFR2 E17-GAB2 E2                      | TPM3 E7-NTRK1 E10 |
| FGFR2 E17-KIAA1967 E5                  | TPR E21-NTRK1 E10 |
| FGFR2 E17-MCU E2                       | ETV6 E5-NTRK3 E15 |

(Continued)
cell lung cancer (SCLC), there is a low incidence of central nervous system metastases amongst limited-stage GEP-NECs; therefore, prophylactic cranial irradiation is not recommended.24 Palliative radiotherapy may be beneficial for either metastatic locations or primary tumour local symptoms. Unfortunately, most NEC patients have disseminated disease at diagnosis. It is mandatory that patients with advanced NEC start chemotherapy as soon as possible before their general condition declines rapidly and they are no longer fit for receiving cytotoxics. To date, it is challenging to assess and compare the results of the different chemotherapy treatments amongst NECs, given the fact that the available evidence is based on small retrospective studies from single institutions. Also, most of the studies present mixed cohorts (e.g. NET G3 and NEC), with a combination of GEP locations, and quite often differ in relation to biological characteristics (e.g. wide range of heterogeneity above Ki-67 index >20%). In 1985, Evans and colleagues established cisplatin and etoposide as the former standard treatment for SCLC, instead of historical and more toxic schemes such as cyclophosphamide, Adriamycin and vincristine (CAV) triplet.53 In light of their biological similarities to SCLC and the lack of well-designed randomized trials, platinum-based doublets were then extrapolated for treating extrapulmonary NECs.54

Since the early 1990s, small retrospective series supported the implementation of first-line regimens based on cisplatin and etoposide.55 The cisplatin and etoposide combination was established as the gold standard for metastatic NECs, based on overall objective responses of 42–67%, and the median duration of responses around 8–9.2 months.29,56 Another platinum salt, carboplatin, was tested as an alternative to cisplatin due to less gastrointestinal, haematological, renal and neurological toxicity.57 To date, several studies suggested that carboplatin can replace cisplatin, as both drugs are comparable in efficacy.58 Furthermore, irinotecan combined with cisplatin emerged as an alternative to etoposide although both schemes have not been directly compared.59,60 Irinotecan is generally the companion choice in Asian patients with SCLC and NEC, as Western populations tend to experience increased gastrointestinal toxicity after irinotecan administration.61 Retrospective data of NEC patients treated with cisplatin and irinotecan showed response rates of 64% and mPFS of 7.3 months at first line, similar to those yielded with etoposide combinations.62 Even though NECs are chemosensitive tumours, they inevitably progress, and second-line strategies have shown scarce efficacy. Rescue chemotherapy for GEP-NECs is not well established. The Nordic NEC study suggested that retreatment with platinum and etoposide could be an option, as up to 42% of patients can achieve restabilization of the disease.63 Small series showed also the effect of temozolamide-based chemotherapy after progression on first line, as metronomic single agent64 or associated with capécitabine.65 Of note, Welin and colleagues reported significant stabilization rates of 71% with temozolamide alone or in combination with capécitabine amongst 25 refractory NEC patients.66 Most of these studies seem to indicate that temozolamide regimens may be more efficient in NEC patients with Ki-67 index <50%.67 In a retrospective study, Hentic and colleagues demonstrated that second line with FOLFIRI regimen was a safe and potentially efficient chemotherapy in NEC patients after failure to platinum etoposide (disease control rate of 62% with mPFS of 4 months).68 However, administration of irinotecan in patients with deranged liver function tests may be a contraindication, and major organ involvement with increased bilirubin levels has shown to predict severe neutropenia. Finally, topotecan has also shown modest antitumour activity in heavily pretreated NEC patients.69 With only 23% of stabilizations, overall prognosis remained very poor with mOS of only 3.2 months.

The close multidisciplinary cooperation of different specialists involved in several therapeutic areas is warranted in order to seek for the optimal therapeutic strategy in each case.

### Molecular insights and novel agents

The molecular features of high-grade NECs have been scarcely understood for many years, thereby limiting the therapeutic options for this rare malignancy. However, the recent development and implementation of next-generation sequencing platforms have unravelled some of the biological insights hidden behind NECs. NECs harbour more proliferative and aggressive clinic-pathologic features,
which largely resemble poorly differentiated gastrointestinal adenocarcinomas. However, translational analysis of a cohort of 25 cases suggested that NECs preserve genomic and epigenetic characteristics inherited from a different cell of origin than the epithelial progenitors of adenocarcinomas. Somatic mutations have been described in 83% NECs, amongst which TP53 is the most prevalent alteration (57%) regardless of the primary site, and KRAS (30%), PIK3CA/PTEN (22%) and BRAF (13%) mutations are also found. Microsatellite instability (MSI) has been found in approximately 10% of gastric and colorectal NECs, and other consistently molecular aberrations, such as Hedgehog, Notch and p16/Rb/cyclin D1 altered signalling pathways, have also been detected. The discovery of potentially actionable targets has widened the therapeutic options for these patients.

BRAF V600E mutations (BRAFV600E) have been described across several malignancies. Hence, efforts have focused on developing targeted agents against this promising driver. Initial encouraging results were reported with BRAF inhibitors in monotherapy although the combination of BRAF and MEK inhibitors showed clear superiority for the treatment of metastatic BRAFV600E melanoma. Klempner and colleagues reported dramatic responses to combined BRAF and MEK inhibition in two cases of colonic NEC harbouring BRAFV600E, after experiencing progressive disease through platinum-based regimens. These initial results provided strong evidence that BRAFV600E is an oncogenic driver in this molecular subset, supporting the rationale for a personalized medicine strategy. However, it is well described that different mechanisms of resistance to BRAF/MEK inhibition may ultimately lead to reactivation of the MAP kinase pathway in these patients, which could explain the transient benefit seen in some BRAFV600E NEC patients treated with dual blockade. Results of the BEACON phase 3 trial, assessing the combination of encorafenib – BRAF inhibitor – plus binimetinib – MEK inhibitor – and cetuximab – EGFR inhibitor – in BRAFV600E metastatic colon cancer, shed some light into the clinical value of this strategy. Thus, the triplet significantly improved median overall survival (mOS 15.3 months) and overall response rate (ORR 48%). In this same direction, Capdevila and colleagues generated a BRAFV600E patient-derived xenograft (PDX) of colonic NEC that was treated with cisplatin-etoposide, encorafenib, cetuximab and the combination of encorafenib plus cetuximab. They identified the mechanism of resistance to BRAF inhibition in NECs through EGFR upregulation, suggesting the potential benefit of dual therapy with BRAF/EGFR inhibition. This fact highlights the complicated role that BRAFV600E might also play in NECs and the need of further deepening into the underlying mechanisms of bypass, to understand which of these patients could benefit most from targeted therapy.

Immune-checkpoint inhibitors (ICI) are arising as a promising strategy within the armamentarium for treating solid tumours. PD-L1 expression has been retrospectively reported amongst 21.9% of patients within a heterogeneous collection of 32 GEP-NEC samples. This PD-L1 expression has been significantly associated with high-grade tumours (41.2% G3 NETs and NECs; p=0.008). Considering that there are limited therapeutic options for NECs, this high proportion of PD-L1 expressors suggests that anti-PD-L1/PD1 blockade might be a useful therapy for this subgroup of tumours. Spartialuzumab, an anti-PD-1 antibody, was tested amongst 21 patients with GEP-NEC after progressing one prior chemotherapy line. PD-L1 expression in immune cells >1% was higher amongst NEC patients (43%), which achieved ORR 5% with a disease control rate of 19%. A refractory pancreatic NEC expressing 30% PD-L1 positivity was also treated with off-label ICI pembrolizumab, another anti-PD-1 antibody, demonstrating a significant partial remission of 66%, that translated into a gain of quality of life and pain relief of the patient. GEP-NECs rarely show MSI although the presence of MSI NECs has been associated with distinct biology and a better outcome. In 2017, pembrolizumab was approved by the US Food and Drug Administration (FDA) for MSI-high/deficient mismatch repair tumours (dMMR) independently of origin, following an agnostic-histology approach. Taking into consideration all these premises, immunotherapy stands as a promising treatment option in a difficult-to-find subgroup of metastatic NECs.

Conclusion

Published data from metastatic colorectal NEC treated with cisplatin and etoposide demonstrated a mOS of 9.5 months, with mPFS of only 4.5 months, similar results to those achieved in our case. Patients with high-grade NECs benefit from multidisciplinary approaches, combining systemic chemotherapy regimens and radiotherapy techniques, and carefully considering rescue surgery in selected cases. Nevertheless, NECs commonly present metastatic dissemination at the time of diagnosis, with no available curative treatment. Despite remarkable advances in the management of NENs, only well and moderately differentiated NET patients can benefit from currently approved tyrosine kinase inhibitors, whilst cytotoxic platinum-containing doublets are the backbone therapy for NET G3, NECs, and MiNENs. Unfortunately, the limited activity provides only short-lasting clinical benefit to many patients. During the last decade, we have progressively acquired a more comprehensive description of the targetable genetic features that characterize high-grade NECs. First, BRAF/MEK-directed therapy has emerged as an exciting option for BRAFV600E NEC patients, and recently, ICI responses suggest that a subset of patient may achieve meaningful benefit from immunotherapy. Treatment for rectal NECs should be highly individualized, based on the tumour burden and symptoms, and the best therapeutic approach for every patient will depend on whether the aim is to slow tumour growth or improve symptoms. There are no currently available defined measures to predict which tumours will or will not respond to treatments, and a major goal in the future will be to identify molecular markers that will facilitate the prediction of the biological behaviour of these tumours. In addition,
given the emergence of functional genomics and expression profiling, both animal and cellular models are needed to investigate further the underlying molecular and genetic biology of NECs. Responses from molecularly targeted agents lack durability, mostly due to adaptive feedback mechanisms that can bypass the blockade or to activate other proliferative pathways. Gaining a deeper knowledge of NEC biology may help a better characterization of NECs, which will ultimately be crucial for optimizing the therapeutic strategy. Physicians should strongly consider performing molecular prescreening panels to all NEC patients, in order to assess potentially actionable targets amongst these patients (MSI/dMMR, PD-L1, BRAFV600E). Collaborative groups, aiming to join efforts in the battle of this unmet medical need, should preferably conduct the future rationalized design of clinical trials with novel drugs.

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**Correspondence:** Ricard Mesia, Medical Oncology Department, Catalan Institute of Oncology (ICO)-Badalona; Badalona-Applied Research Group in Oncology (B-ARGO)-Germans Trias i Pujol Institute (IGTP); Germans Trias i Pujol University Hospital (HUGTIP); Crta. de Canyet s/n, 08916 Badalona, Barcelona, Spain. rmesia@iconcologia.net

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